3D Printing in the Catalysts of Batch and Flow Reactions

Dial-a-Molecule

Annual Meeting 2017

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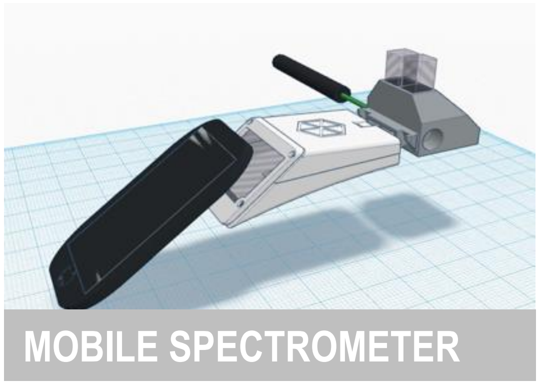
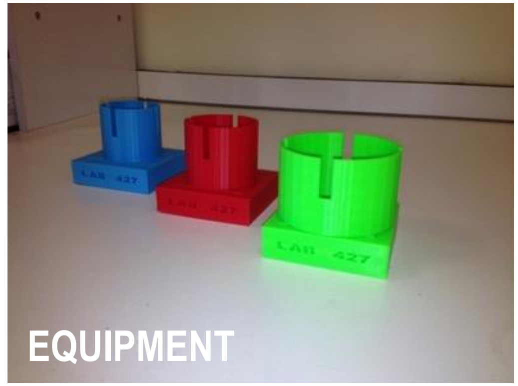
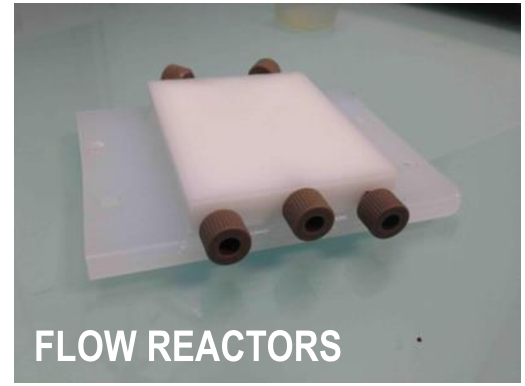
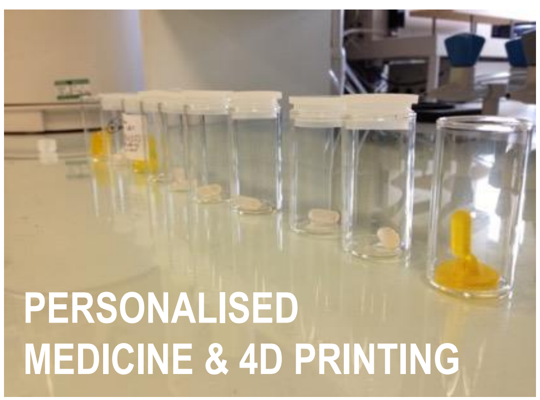
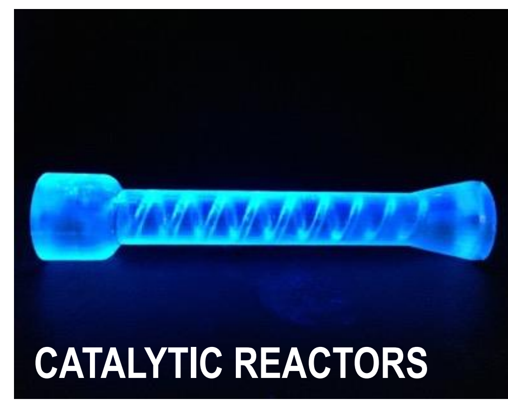
3D Printing Research in the Group





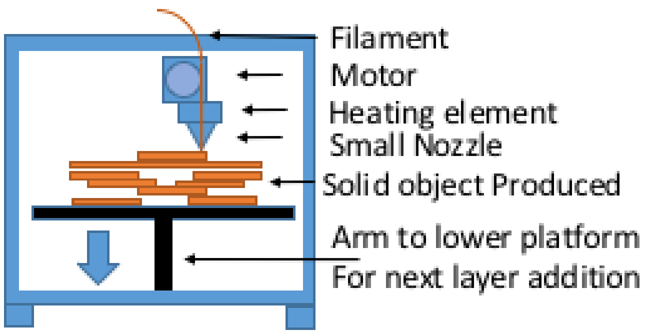




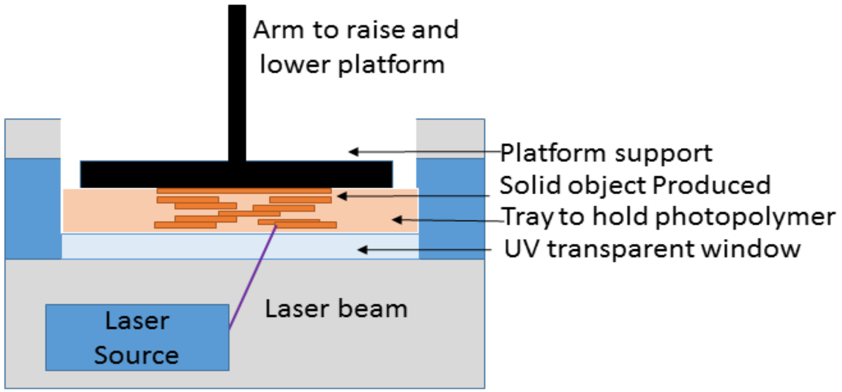


3D Printing Process

FDM Printing

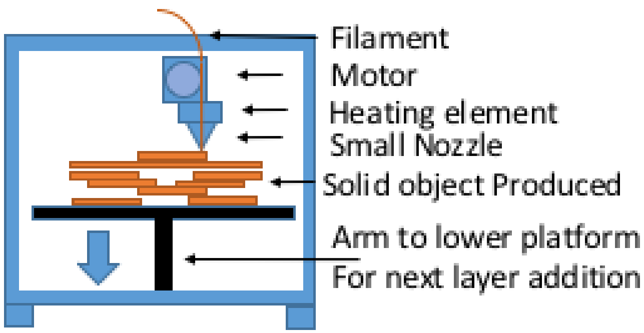


SLA Printing

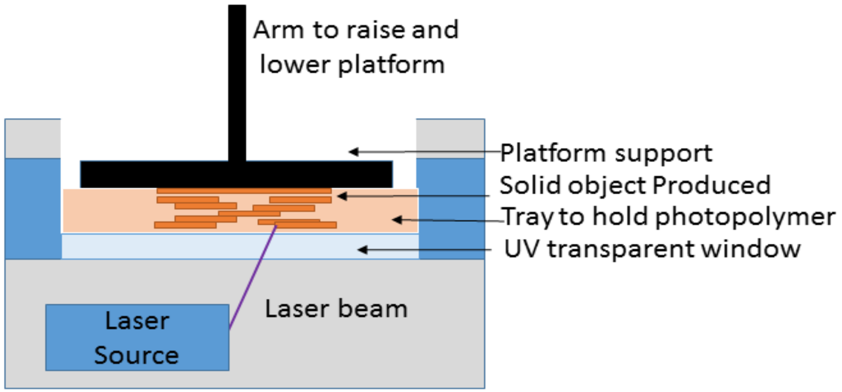


3D Printing Process

FDM Printing

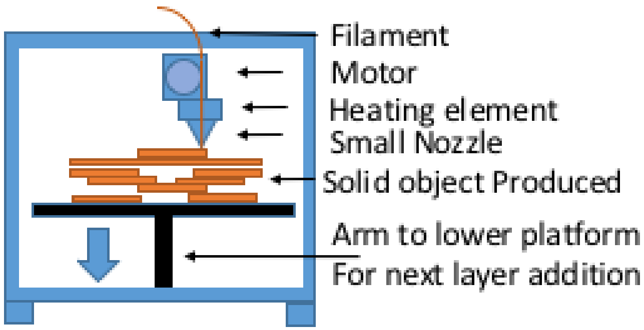


SLA Printing

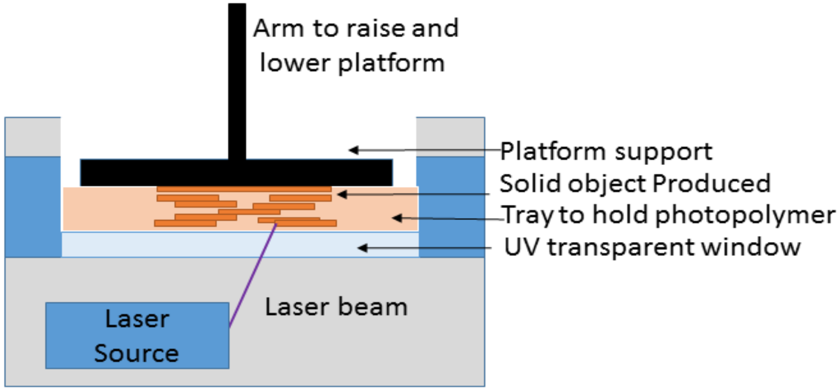


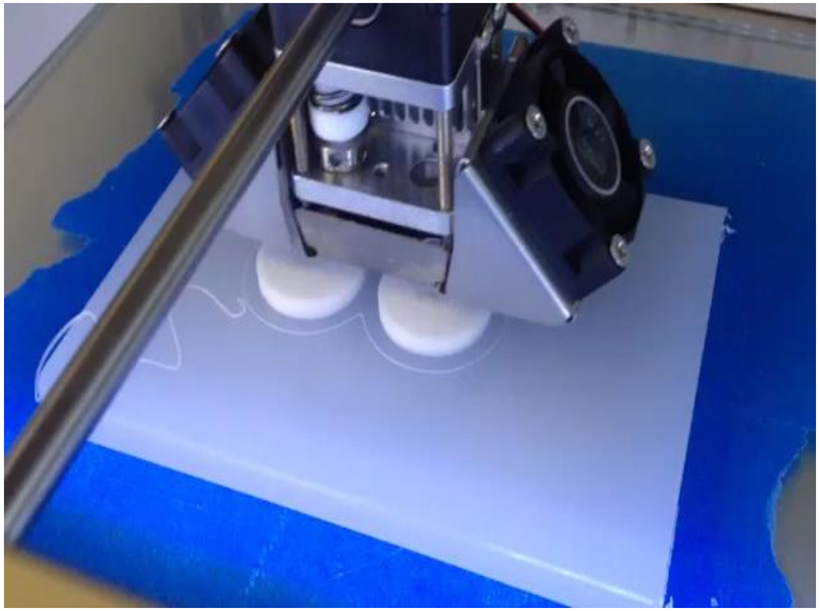
3D Printing Process

FDM Printing

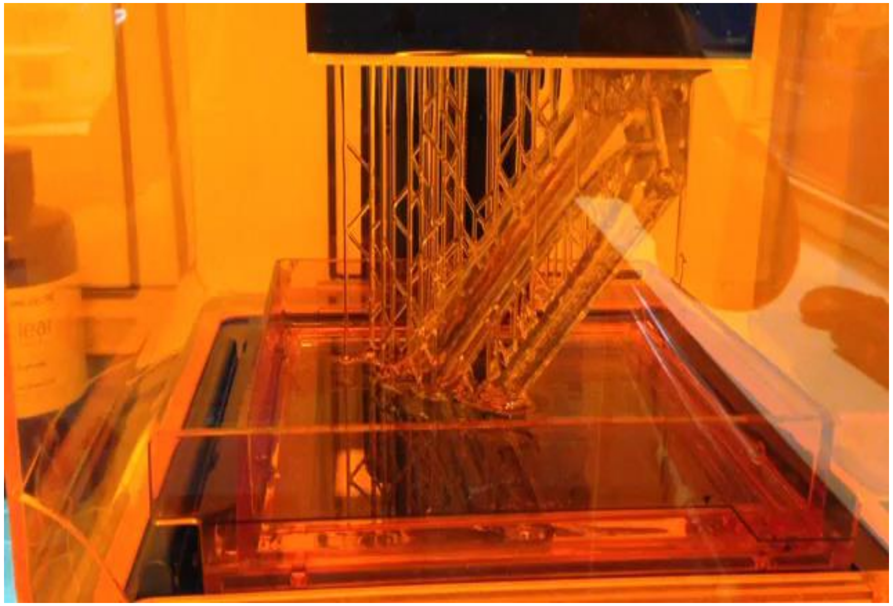


SLA Printing





Fused Deposition Modelling (FDM) Printers

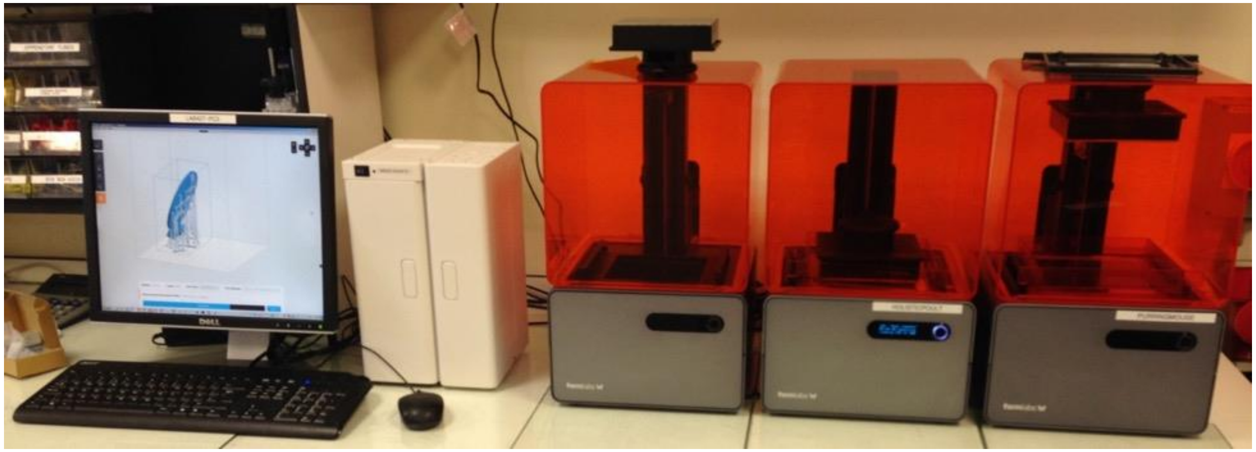


Stereolithography (SLA) Printers

3D Printing Infrastructure

Total of 17 3D Printers

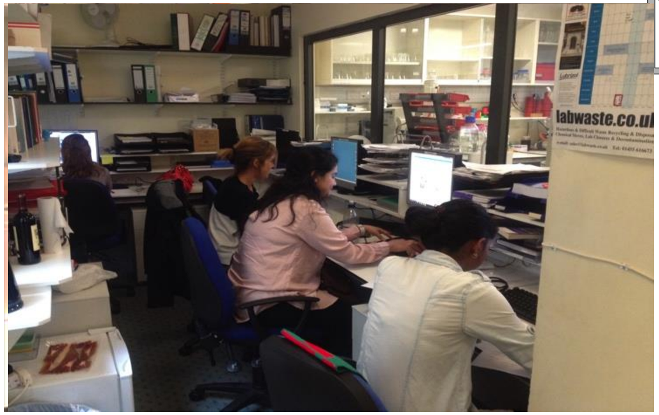
Makerbot Mini
Makerbot Mini+
Ultimaker 2 and 3
Makerbot Replicator 2X
Miicraft
FormLabs Form 1+
FormLabs Form 2
3Drag

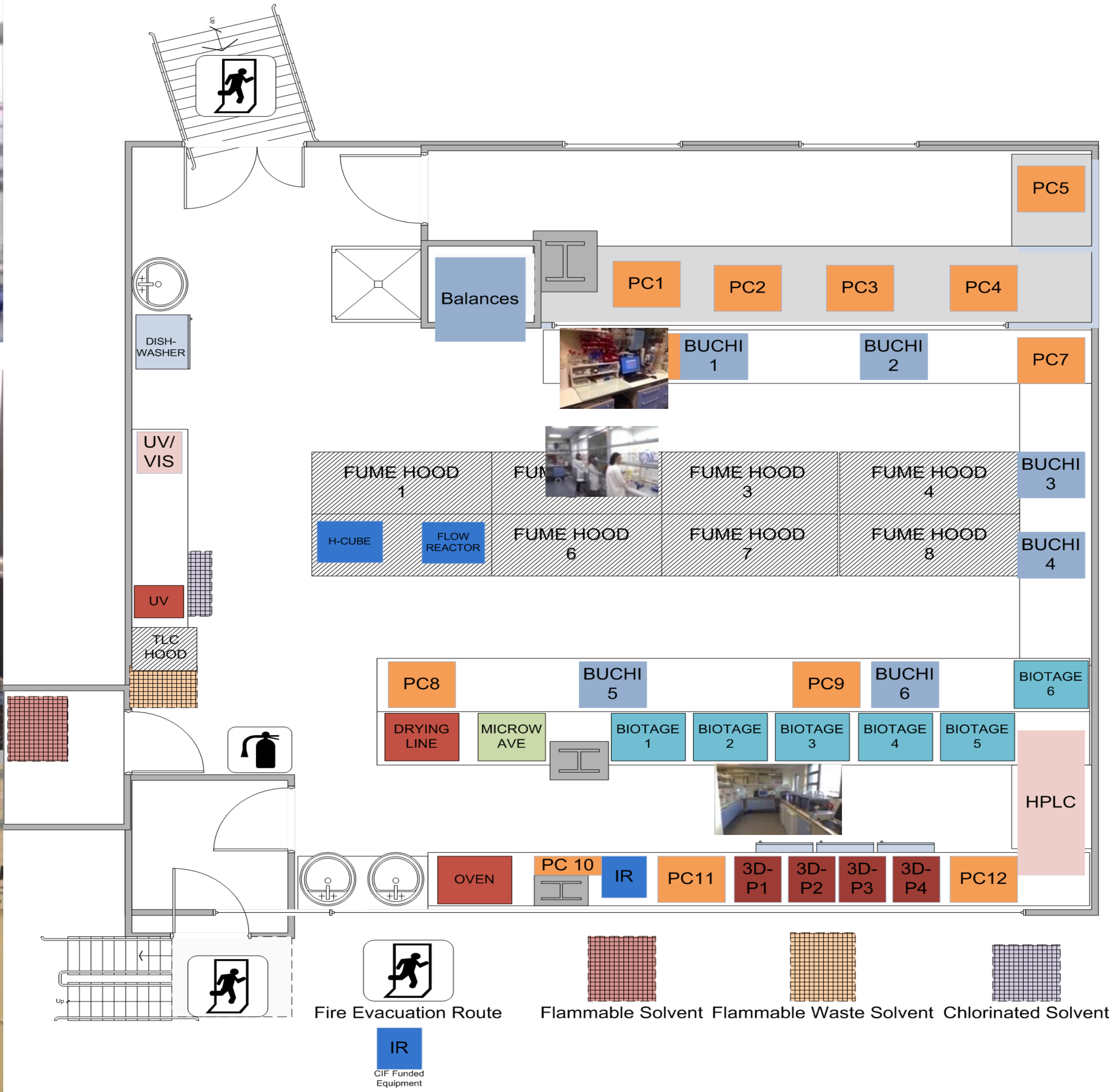


Stereolithography (SLA) Printers

Fused Deposition Modelling (FDM) Printers

3D Printing and Infrastructure





3D Printing Chemistry Targets

Complex Chemistry

Heterocycle Formation

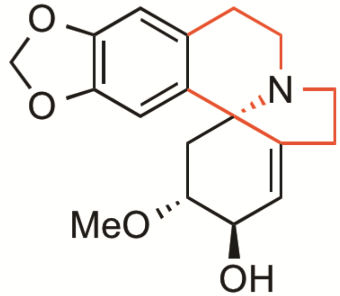
Flow / Batch Chemistry

Scale-up synthesis

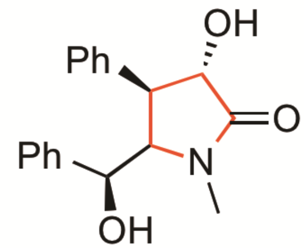
Reproducible

Catalysis

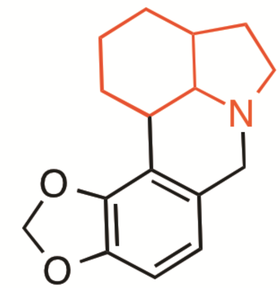
Reusable technology



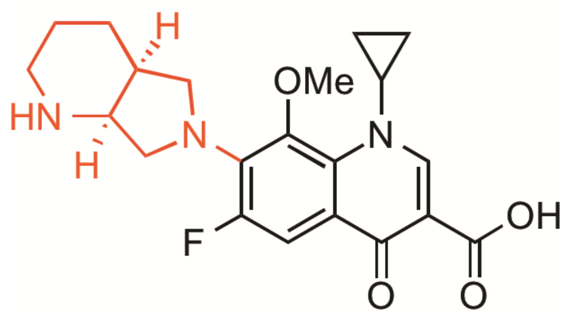
Erythratin



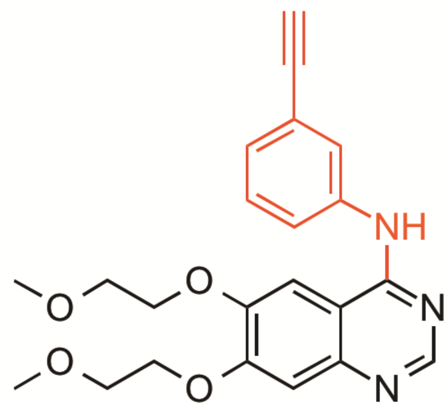
Clausenamide



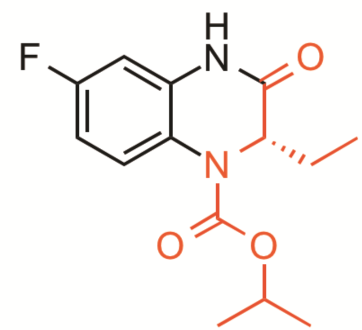
γ Lycorane



Moxifloxacin

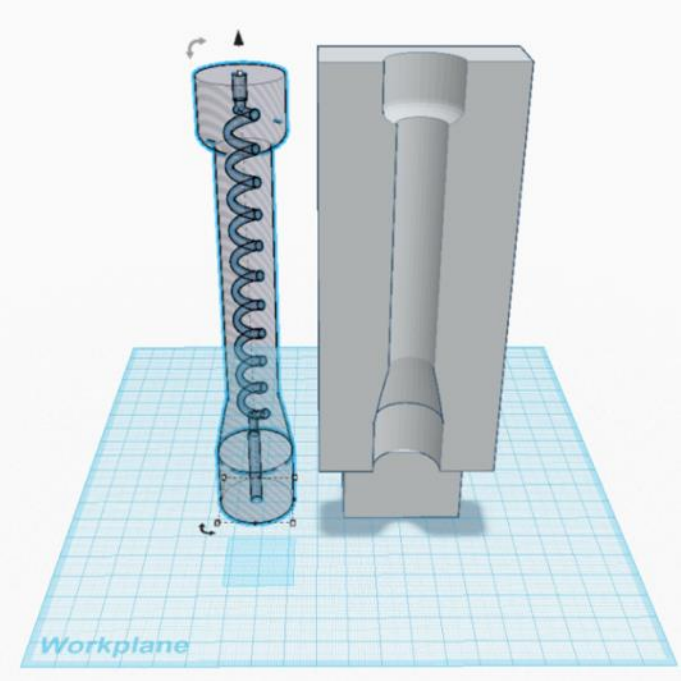


Erlotinib



Quinoxaline core

3D Printing – Continuous Flow



Develop reactors to take the place of the glass column reactor

3D Printing – Continuous Flow

Flow Chemistry - 3D Printing for prototyping/ reactions

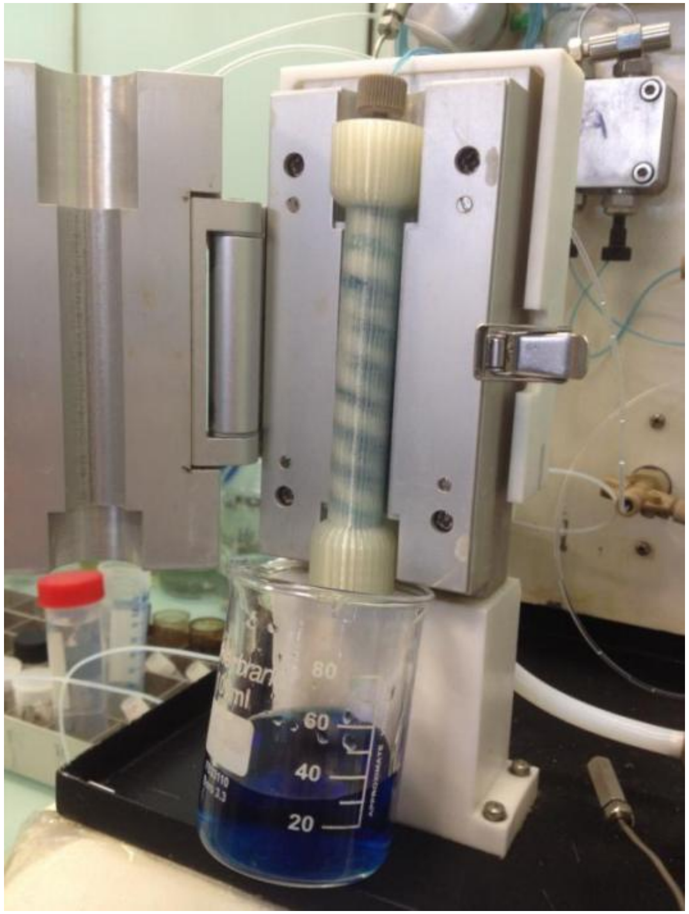
Design based on long contact time with the heated element as shown

Unable to be produced using conventional technology

Prototype shown is in PLA

Printed at 100% infill, 9 shells

100 Micron accuracy



3D Printing – Continuous Flow

Flow Chemistry - 3D Printing for prototyping/ reactions

Reactor printed in polypropylene

Total weight = 21 g
Internal volume = 1.6 mL

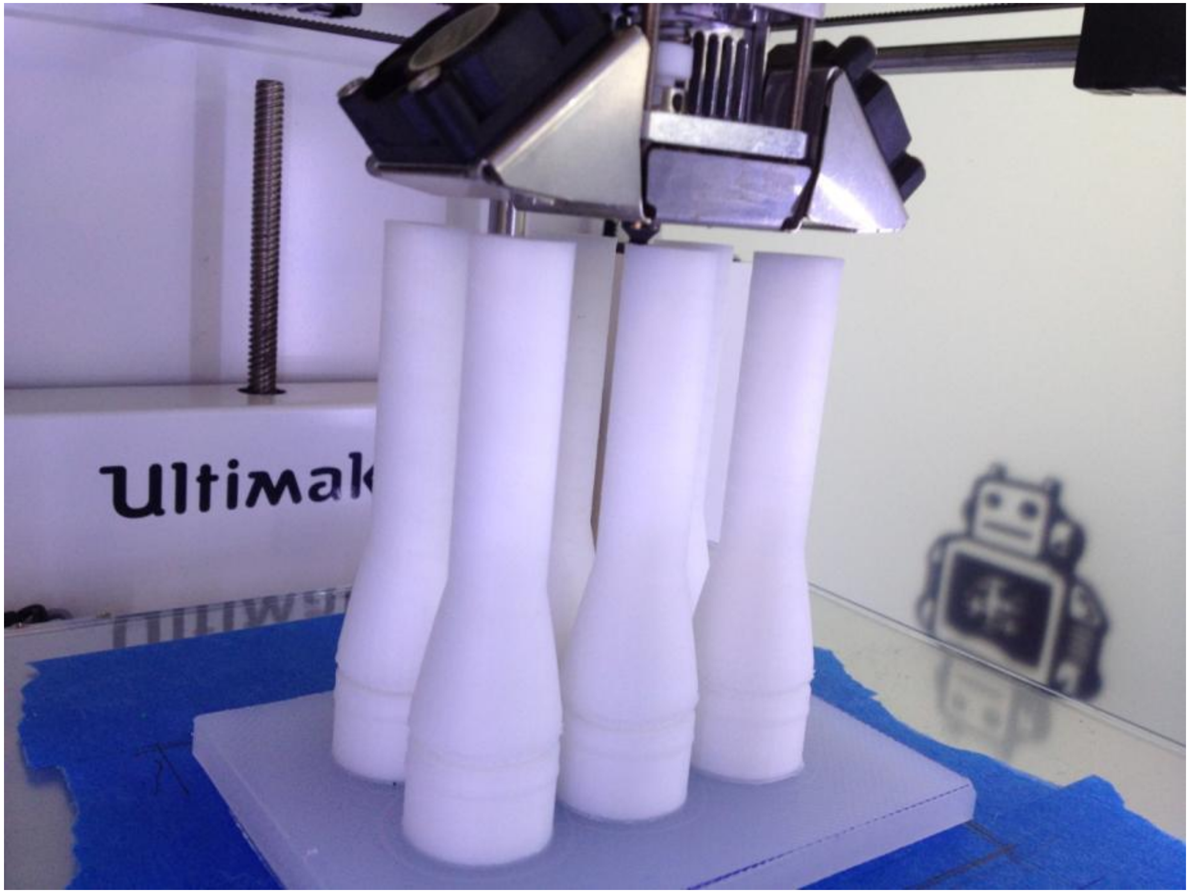
Print time 6 hours

Material flow 110%

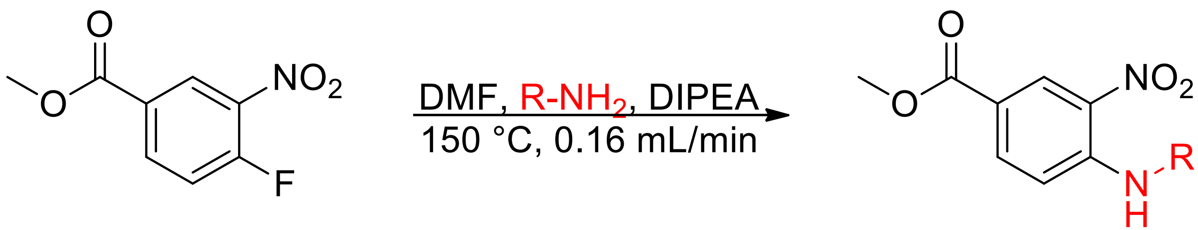
Capable of being heated to 150 C

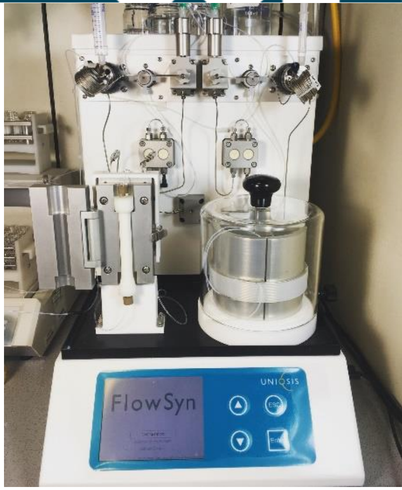
Cost per reactor = £0.56

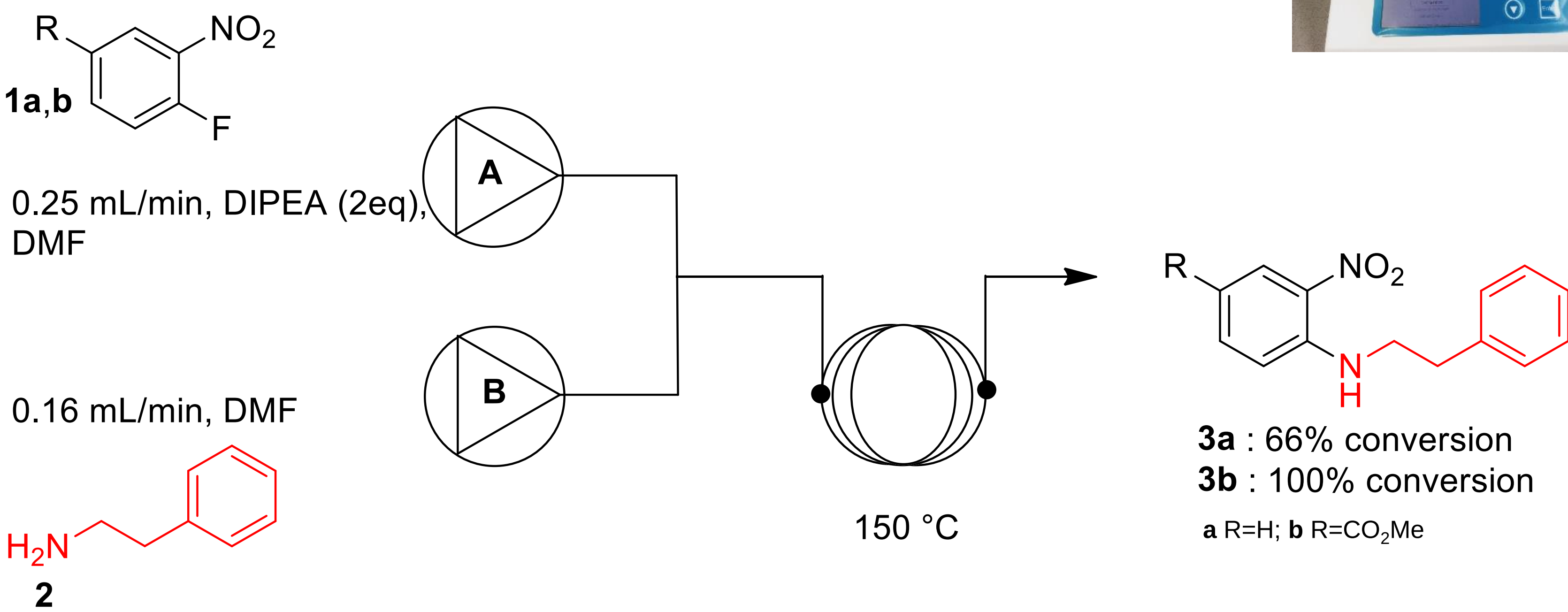
glass reactor column = £180



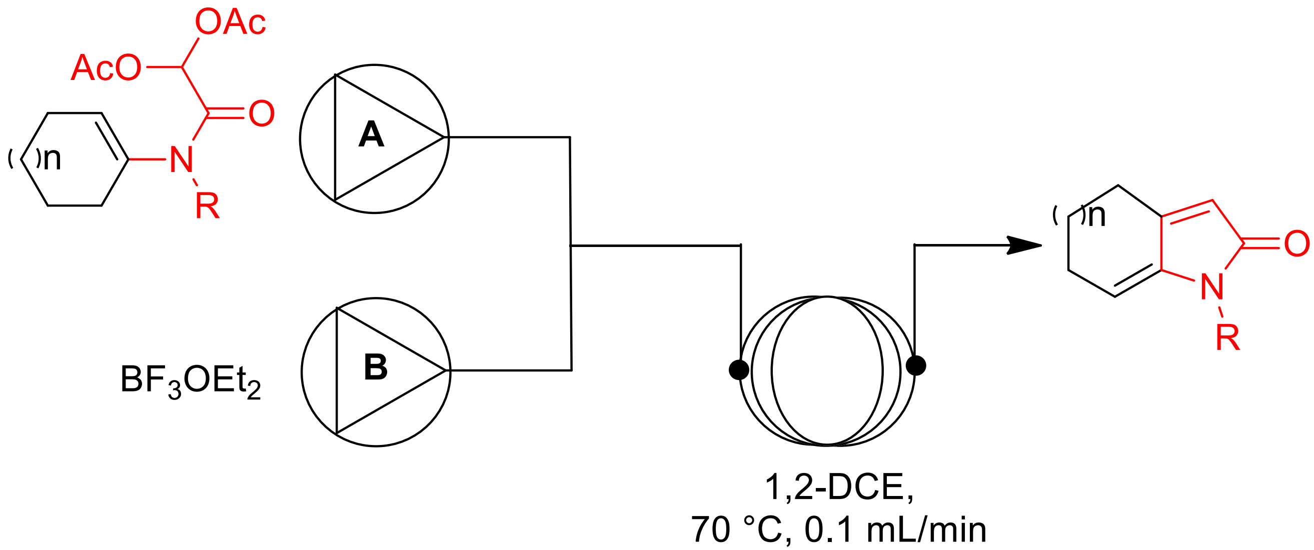
3D Printing – S_NAr

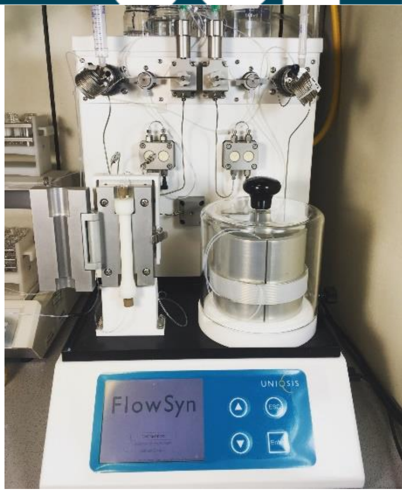


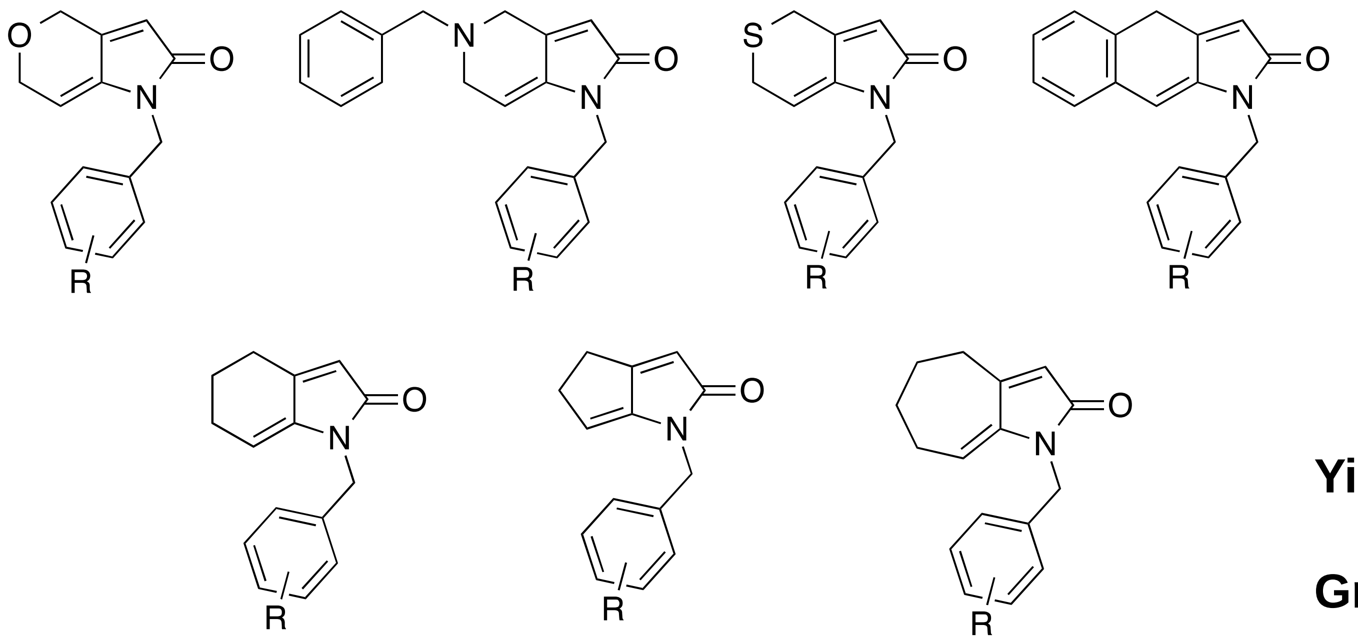




3D Printing – Heterocycles







Yields 40-70%

Gram scales

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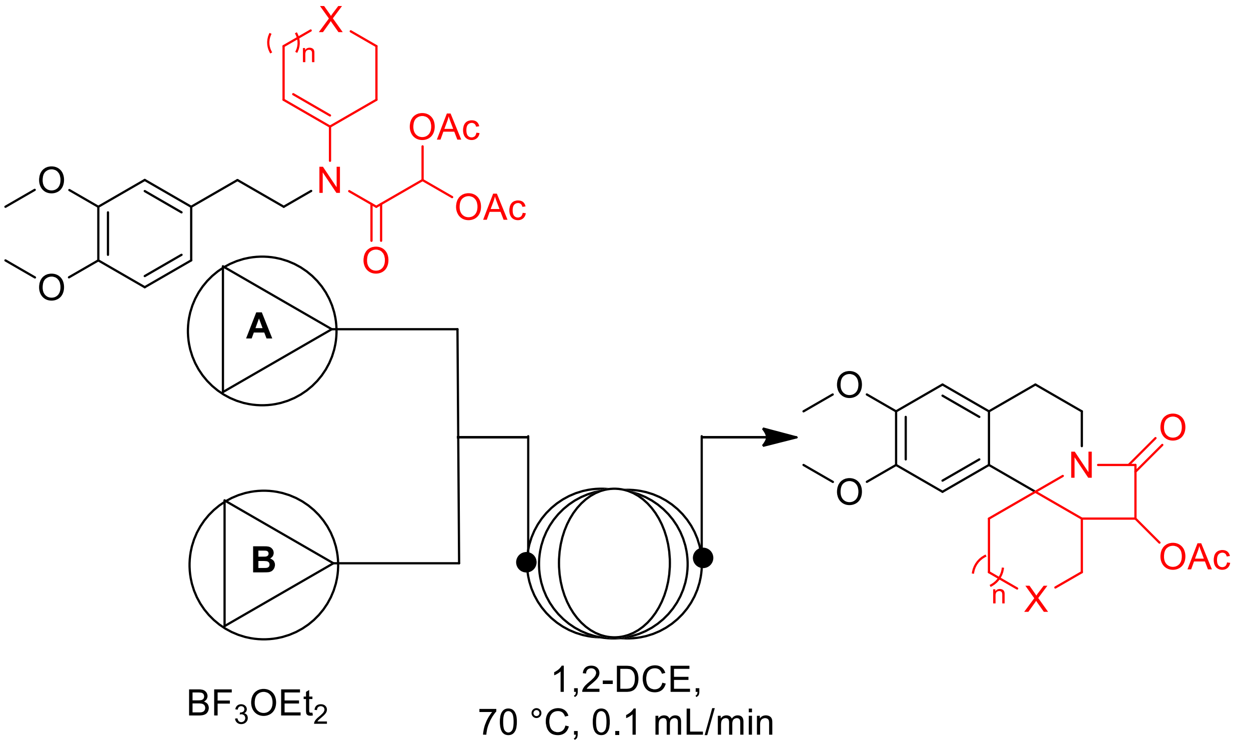
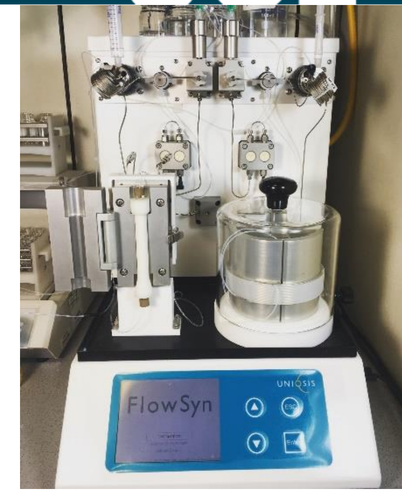
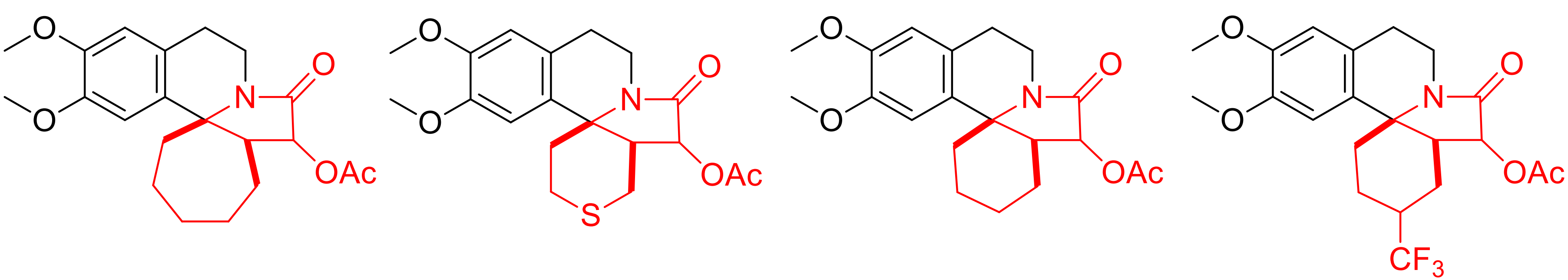
3D Printing – Heterocycles





Yields 50-80%

Single Diastereisomer



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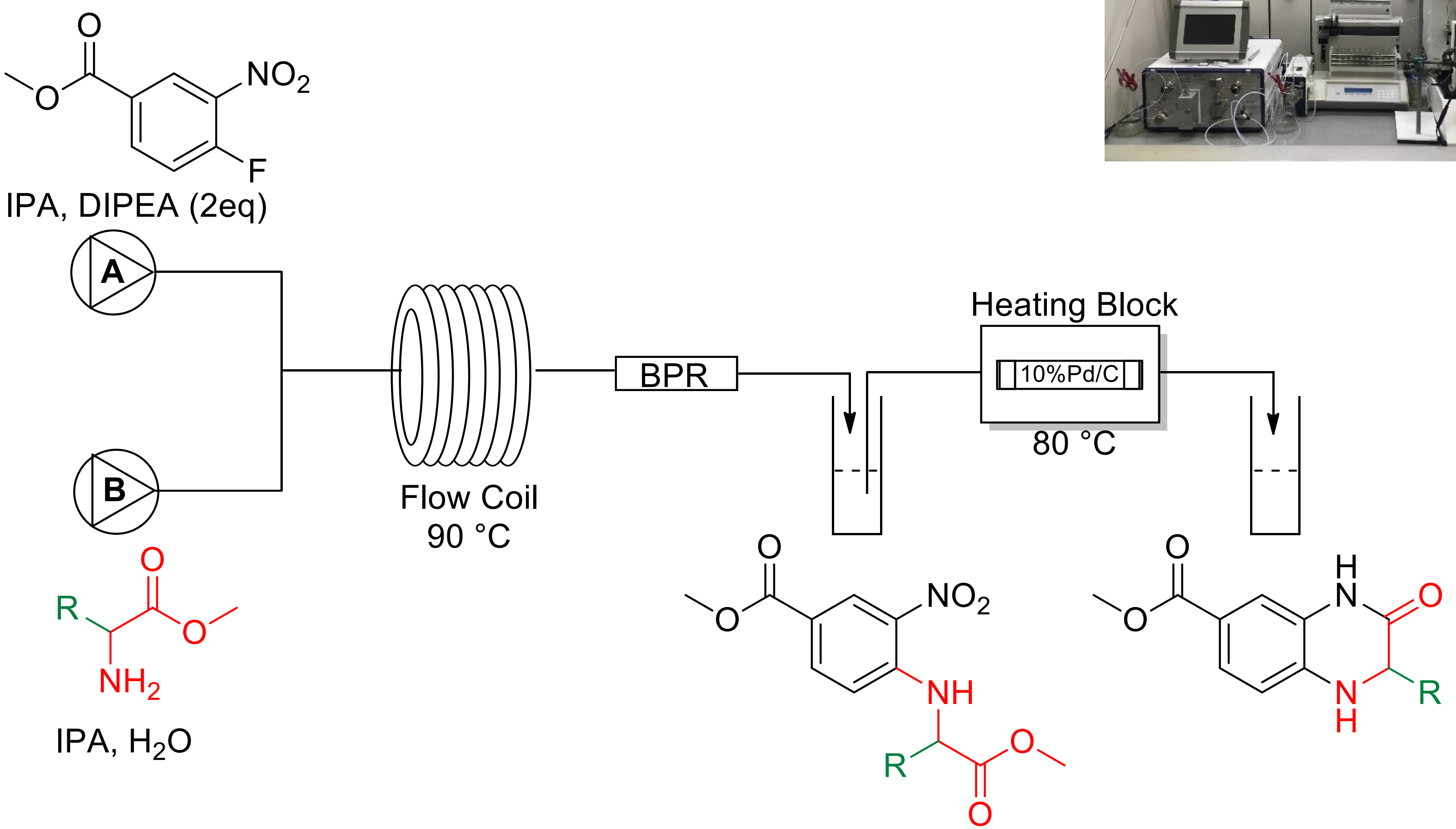
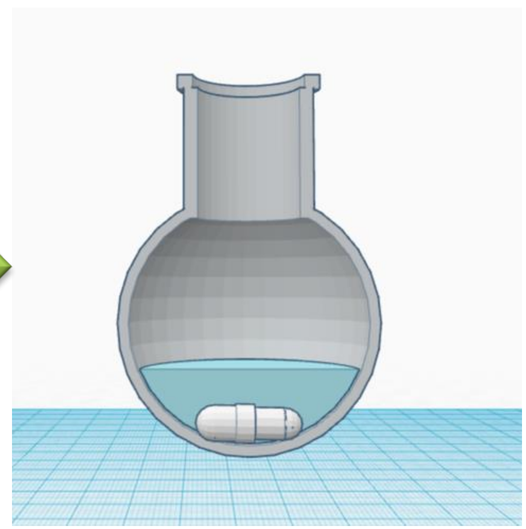
3D Printing – Quinoxalinones

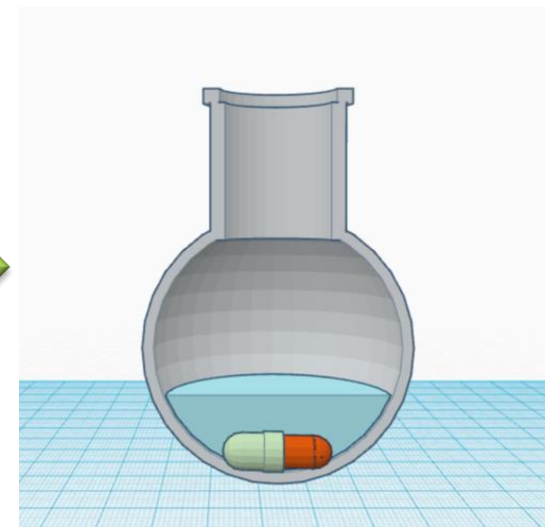
Flow Chemistry - 3D Printing – extension to Hydrogenation



3D Printed Inert reactors

3D Printing Catalysis in Batch Chemistry

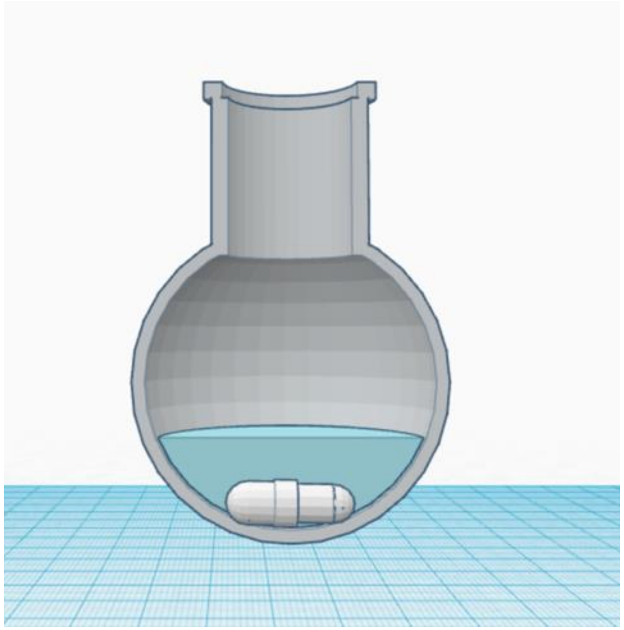


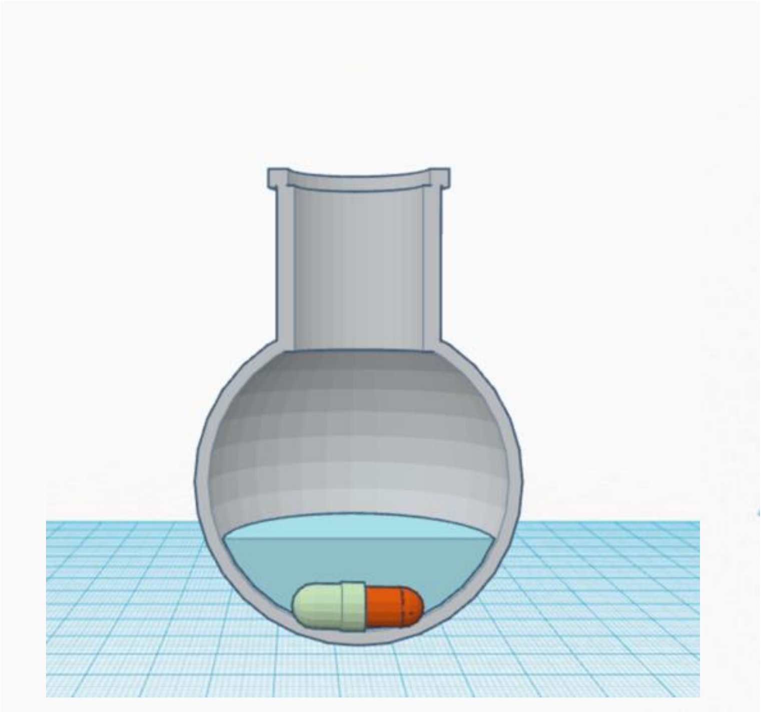


Concept of catalytically active stirrer beads incorporating range of catalysts using FDM Printing

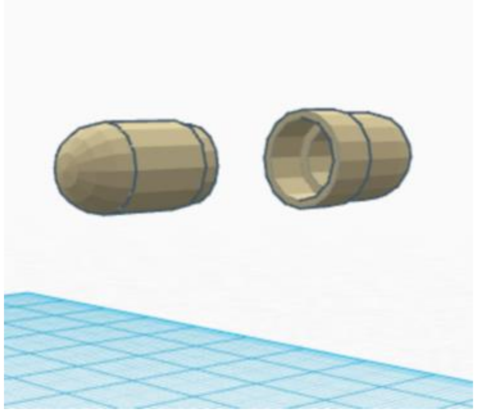
3DSynthesis Catalytic Stirrer Beads

3D Printing Catalysis in Batch Chemistry



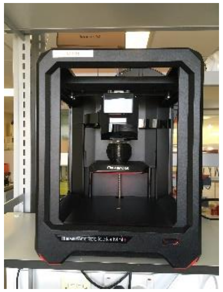


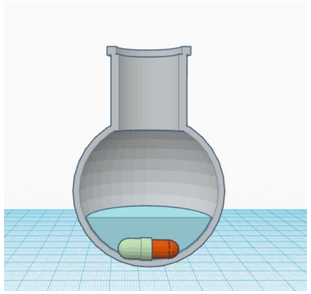
Concept of catalytically active stirrer beads incorporating range of catalysts using 3D Printing

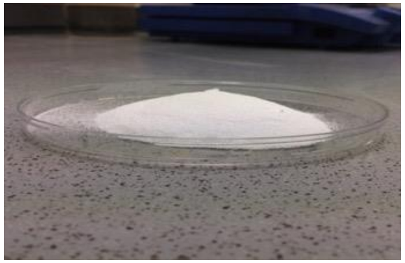


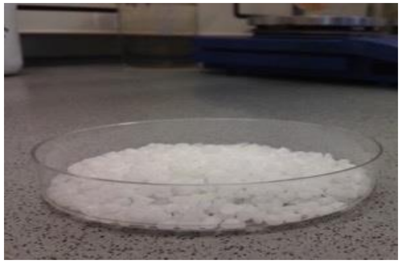
Catalysis via Hot Melt Extrusion

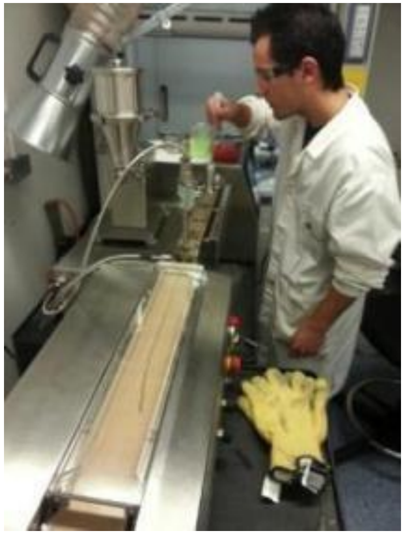
FDM Printing

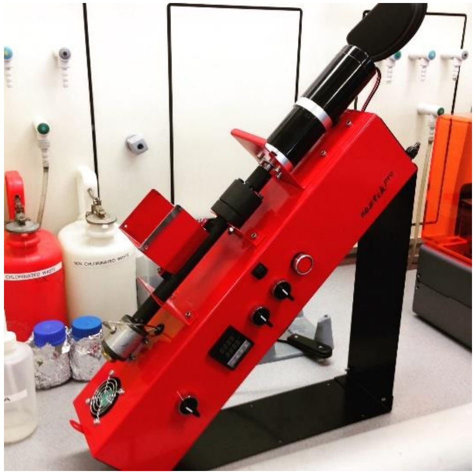






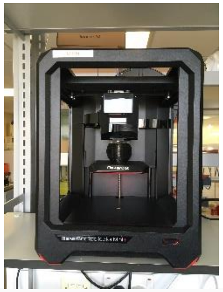


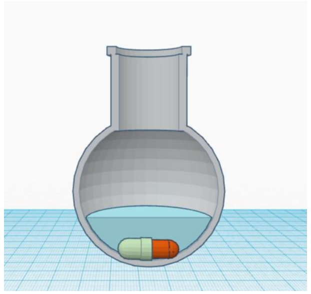


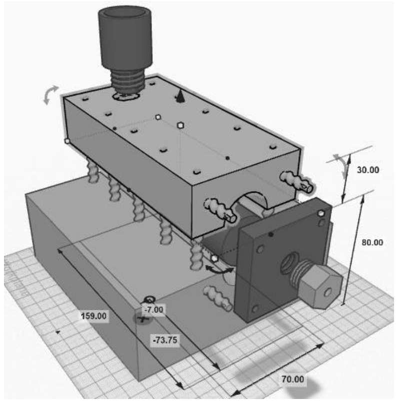


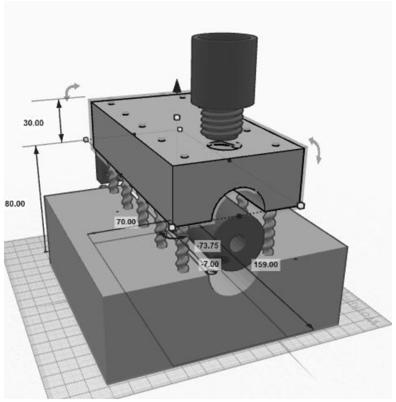
Catalysis via Hot Melt Extrusion

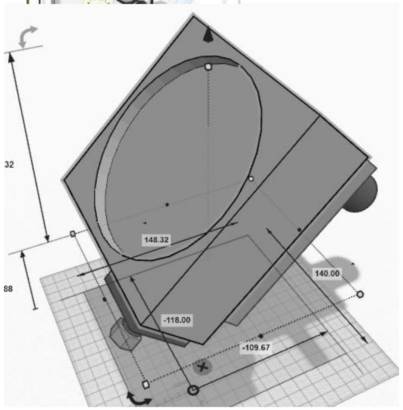
FDM Printing

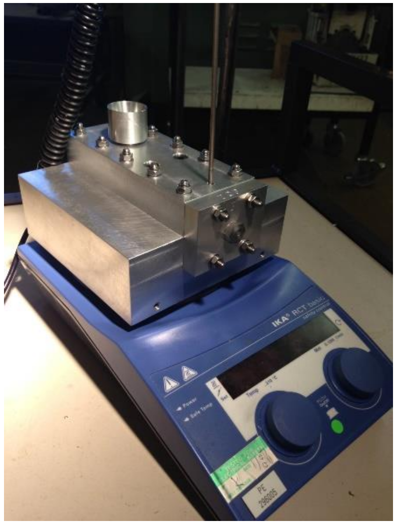


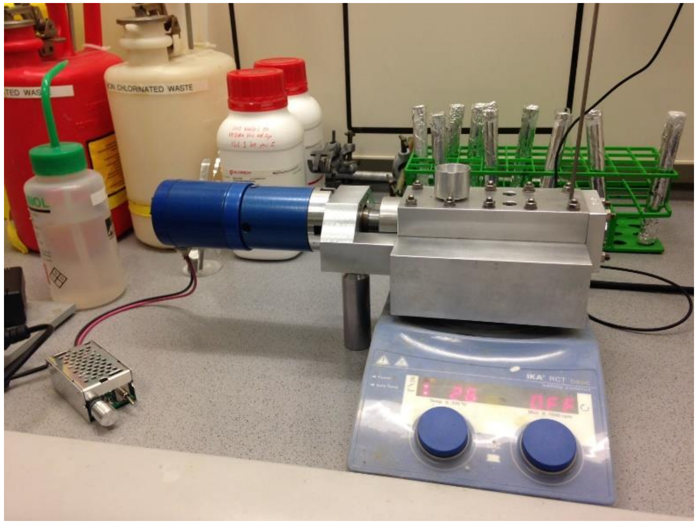






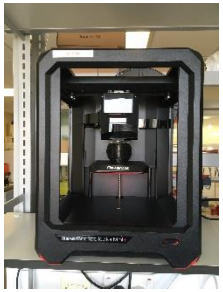


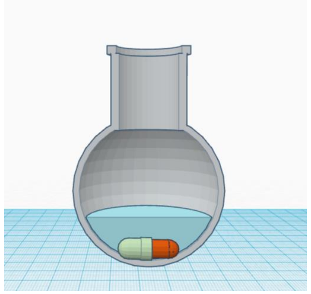


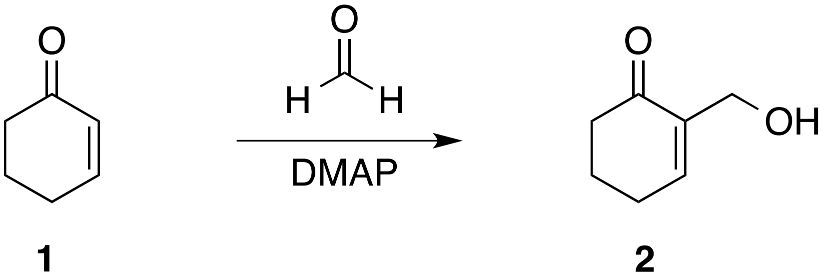


3DSynthesis Catalytic Stirrer Beads

3D Printing Catalysis in Batch Chemistry- Incorporation of DMAP into Polypropylene using FDM Printing







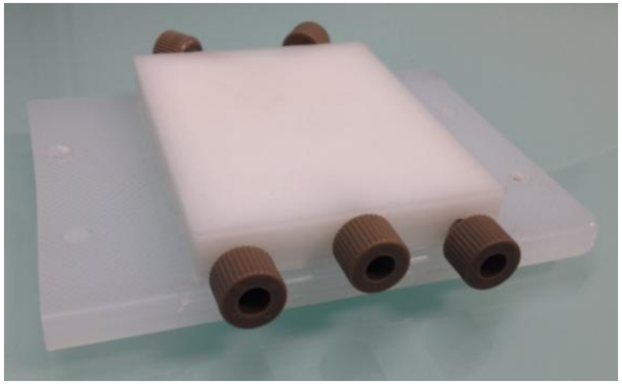
Yields: 50-80%

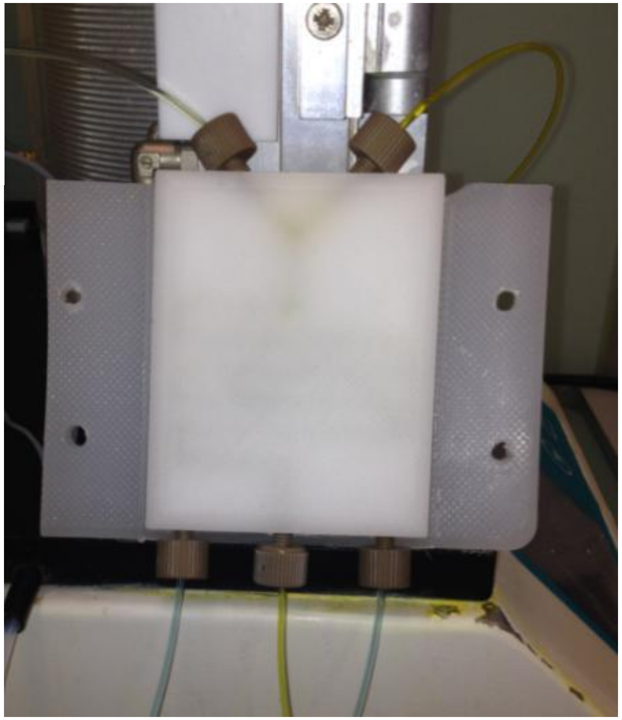
Bruno Sil, Bhaven Patel

3D Printing – Catalysis

Reactor Design crucial
FDM Printing uses Polypropylene and PVDF as inert polymers

Incorporation of catalysts
Extension to SLA would increase resolution and utility - 25 micron – Problem of Solvent Resistance





Matthew Penny

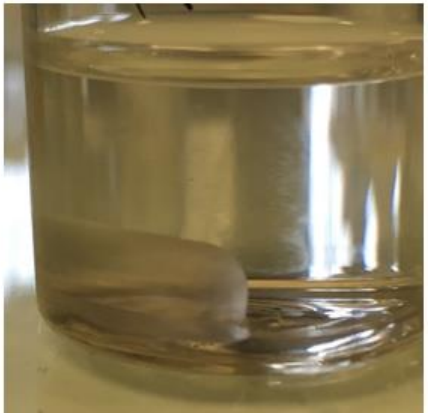
Chemically Resistant Photopolymer

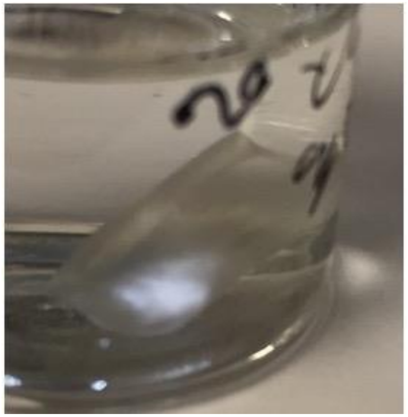
Stereolithography (SLA) Printing gives greater access to complex structures

Challenge of solvent resistance

Standard Resins

Solvent resistant formulation

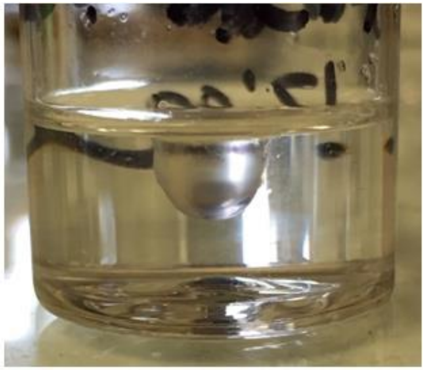




12 h

18 h

48 h



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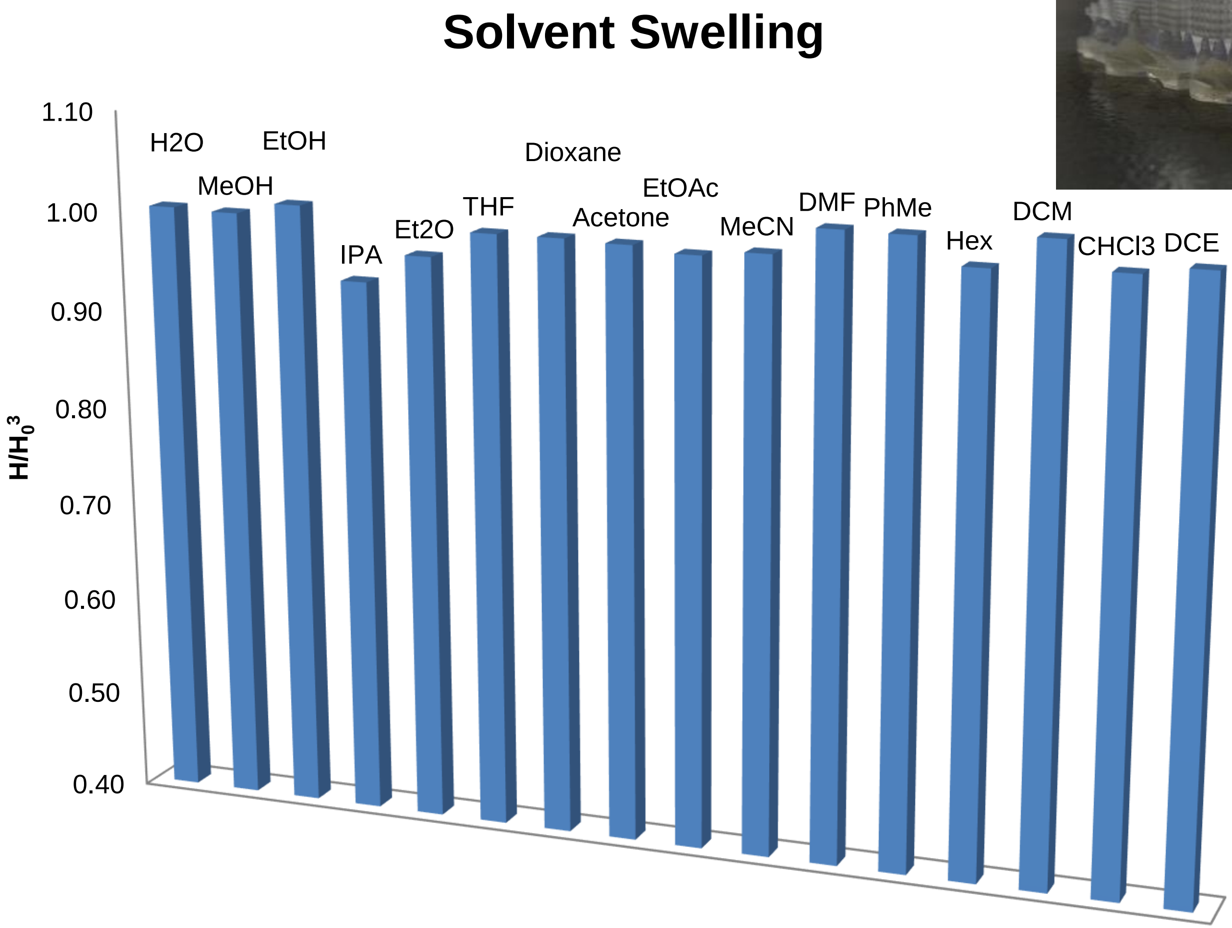
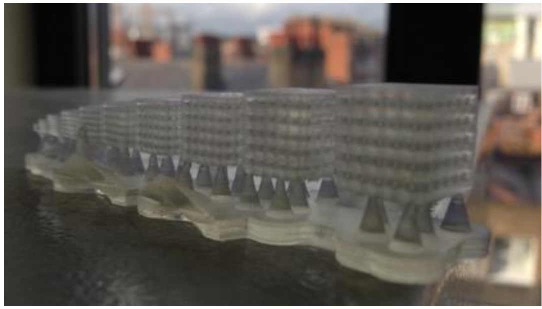
Chemically Resistant Photopolymer





Matthew Penny

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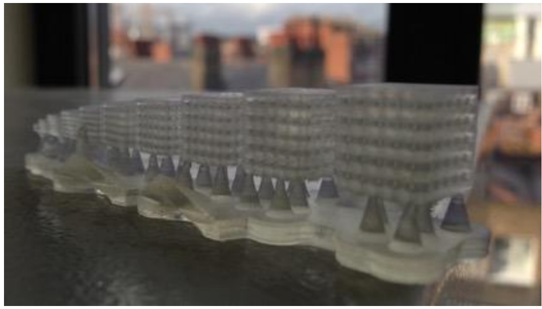
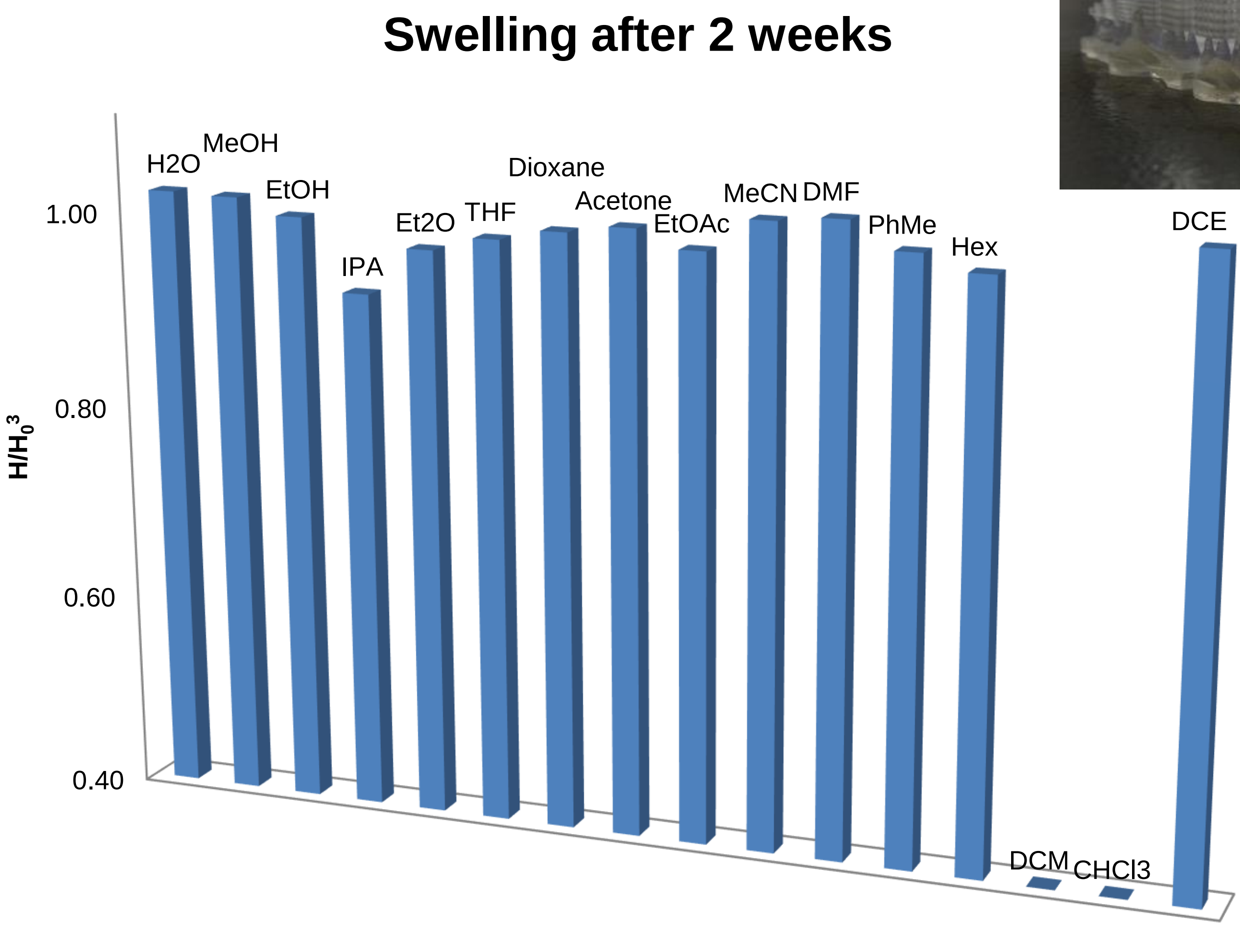
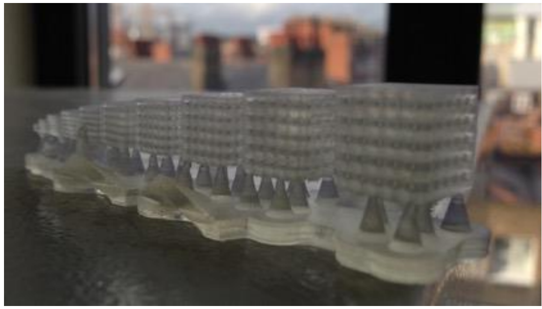


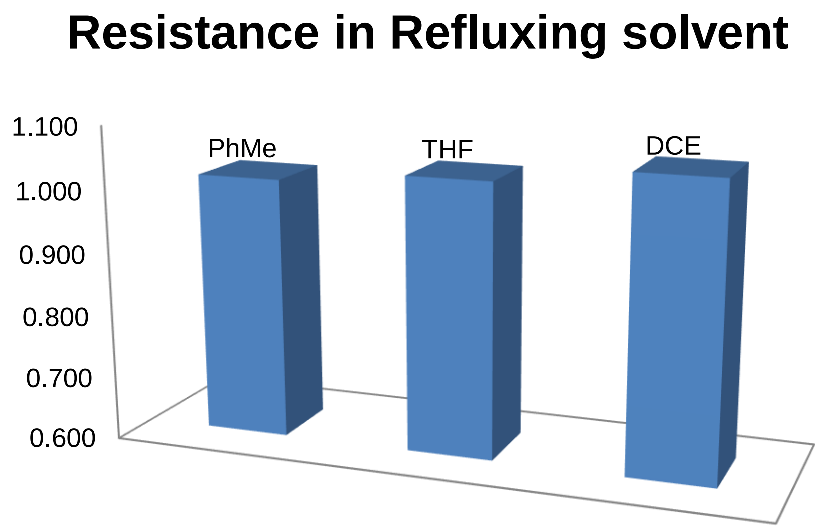


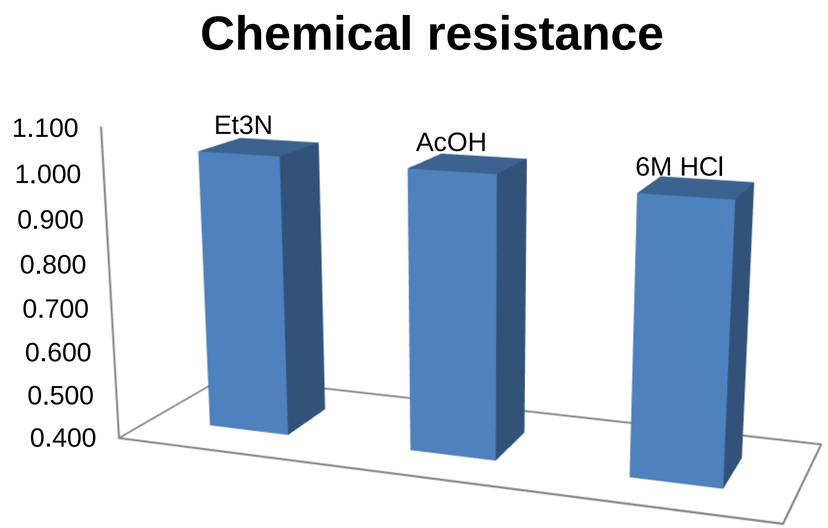
Matthew Penny

UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE

Chemically Resistant Photopolymer



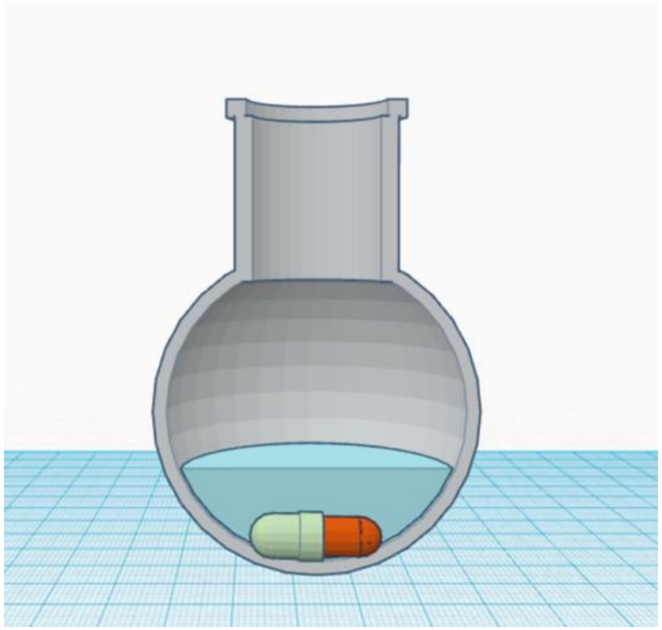


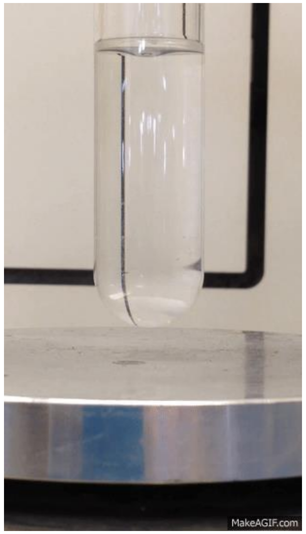


Matthew Penny

3DSynthesis Catalytic Stirrer Beads

- Sterolithography (SLA) printing
- Shape designed to maximise surface area
- and solvent mixing
- Catalyst loading between 5-10% (w/v)
- Resistant to nearly all solvents





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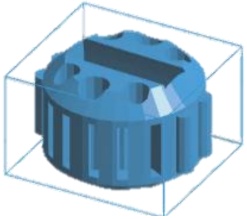
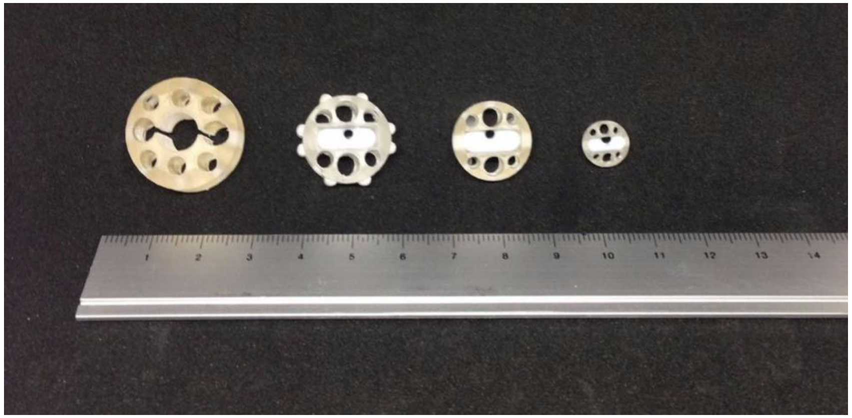
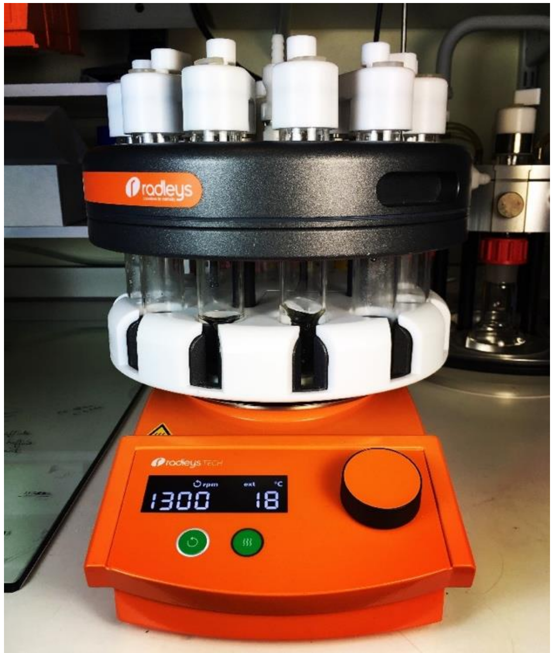
3DSynthesis Catalytic Stirrer Beads



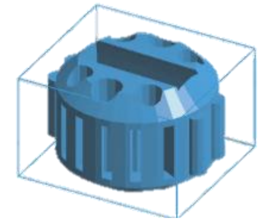
Redesigned for a range of reaction sizes:

- Microwave
- Radleys Carousel
- Round Bottom Flask
- Larger Batch Scale





Efficient Mixing of Reactions

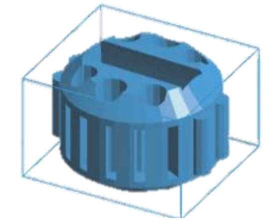


Increased Vortex and mixing of solution

Normal Stirrer

3DS Stirrer

Catalytic Stirrer Beads – Reactions



Reaction Classes

Lewis Acid Catalysis

Mannich

Hantzsch

Heterocycle Formation

Copper Catalysis

Click Chemistry

Chan Lam

Palladium Catalysis

Suzuki

Sonogashira

Heck

Base Catalysis

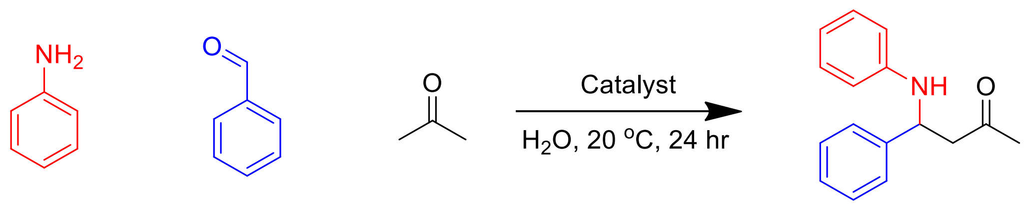
Acylation

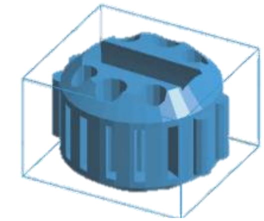
Amide Formation

Matthew Penny

Catalytic Stirrer Beads - pTsOH

Mannich Reaction



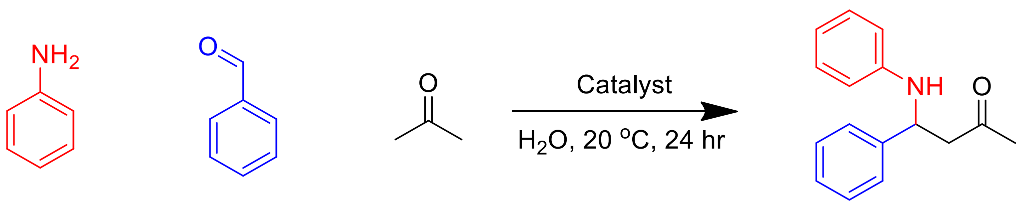


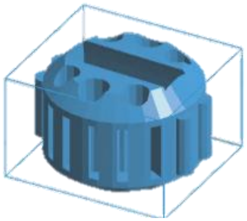
	Yield (%)
5% pTsOH impregnated stirrer bar	84
pTsOH impregnated stirrer bar (2nd use)	81
TsOH	84
No catalyst	20

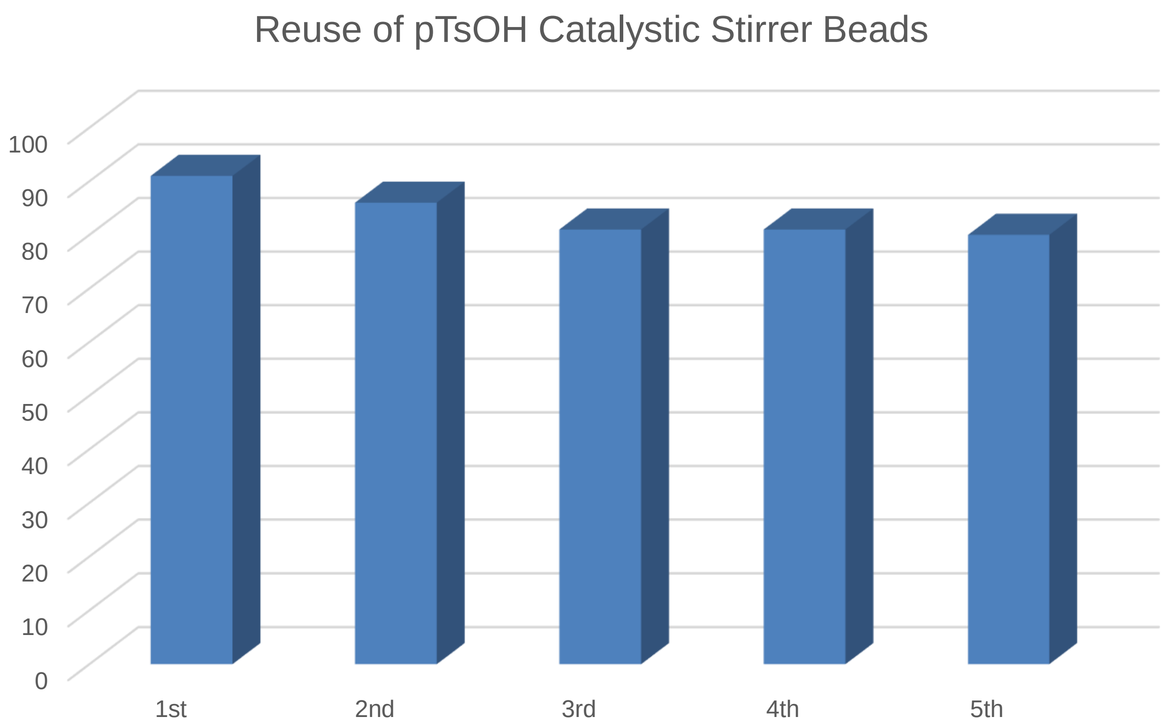
Matthew Penny

Catalytic Stirrer Beads - pTsOH

Mannich Reaction







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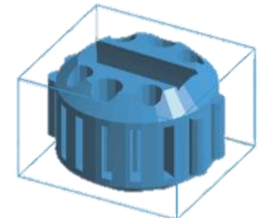
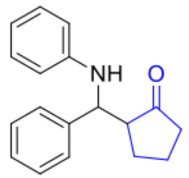
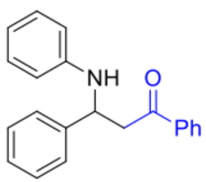
3DSynthesis Catalytic Stirrer Beads

Mannich Reaction

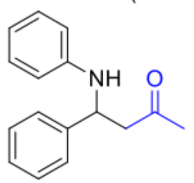




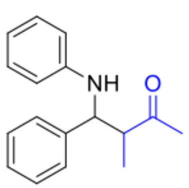
No reaction with stirrer
or free pTsOH



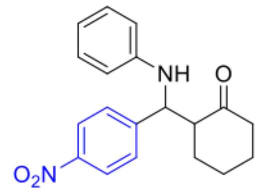
52% (24 h)
47%
22% (20 h)
0% (water)



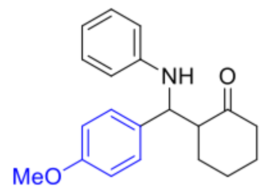
65% (3 h)
17% (22 h)



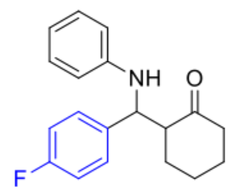
<20%



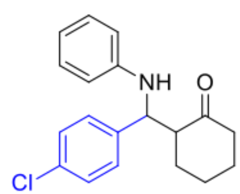
89%



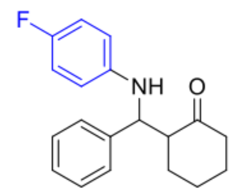
71%



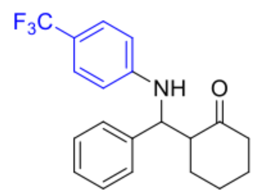
85%



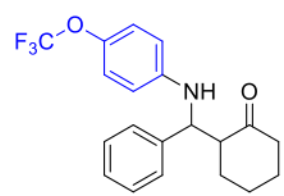
70%



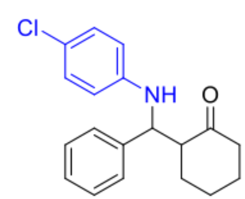
84%



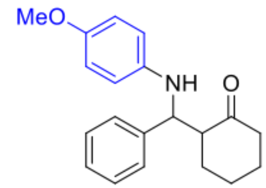
60%



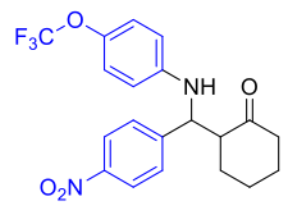
87%



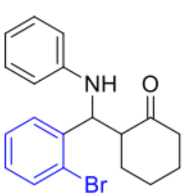
72%



55% product rapidly degradaded



91%



43%

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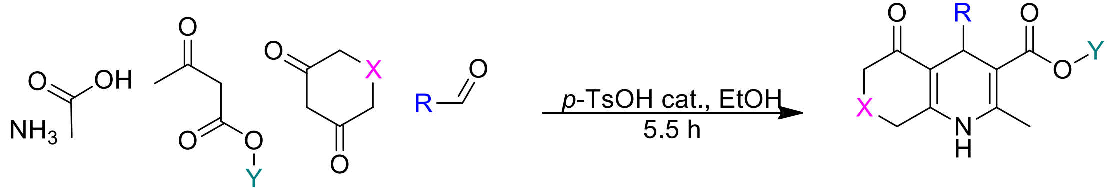
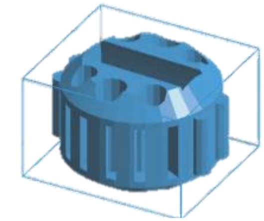
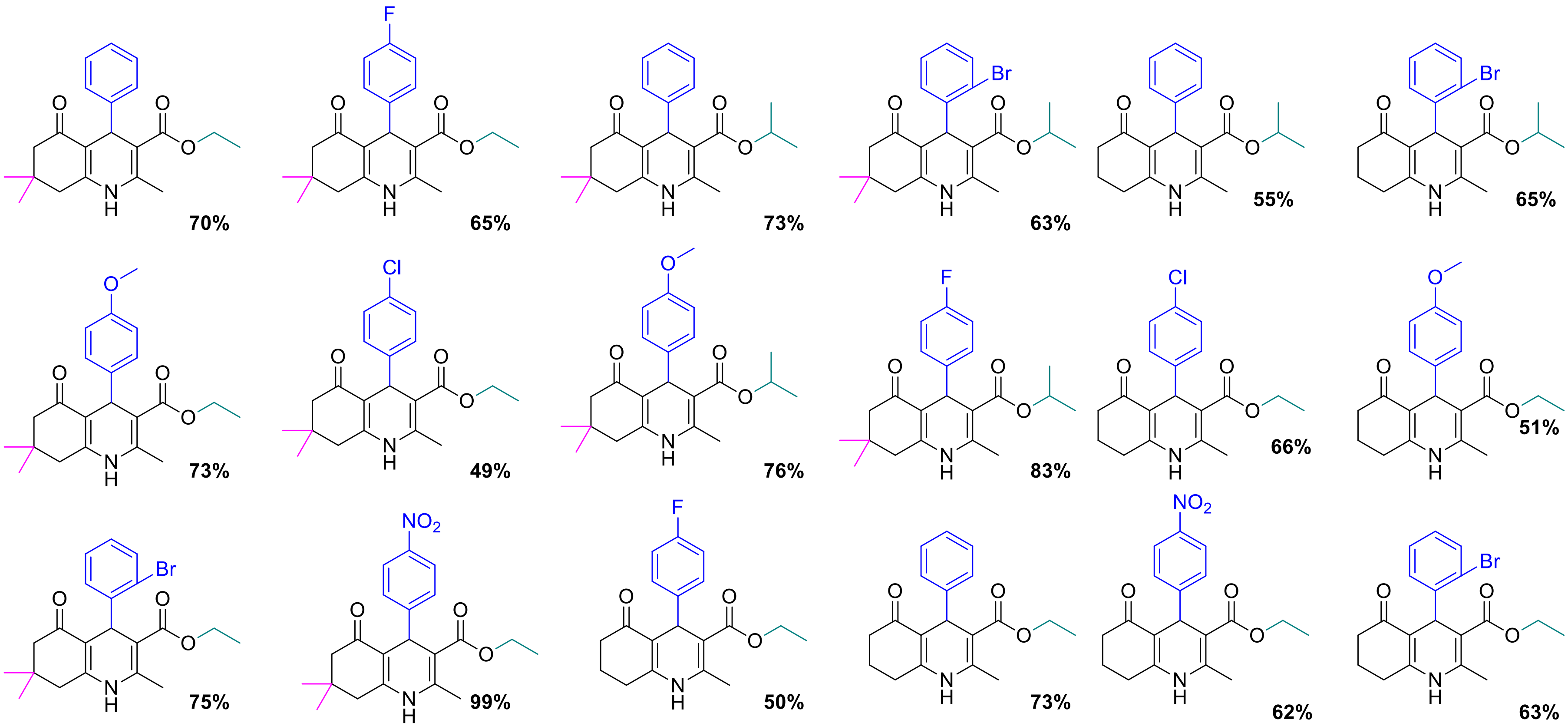
3DSynthesis Catalytic Stirrer Beads

Hantzch Synthesis



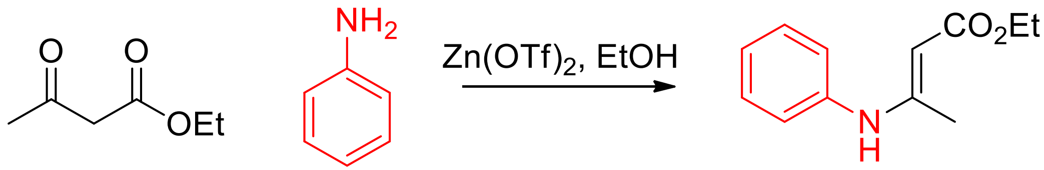


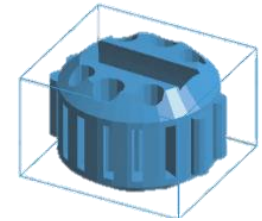


Zenobia Rao

3DSynthesis Catalytic Stirrer Beads

Heterocycle Formation



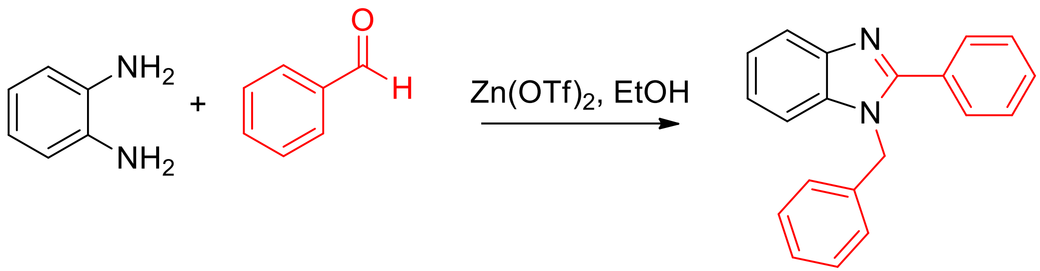


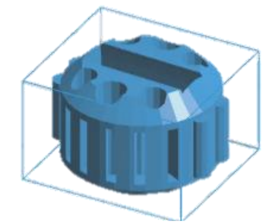
Entry	Reaction Time (hr)	Yield (%)
3D Stirrer Bead + No Catalyst	5	28
Normal Stirrer + Powdered Catalyst	2.5	60
3D Stirrer Bead + Powdered Catalyst	2.5	70
Catalyst Impregnated Stirrer Bead	5	86

Rumintha Thavarajah

3DSynthesis Catalytic Stirrer Beads

Heterocycle Formation



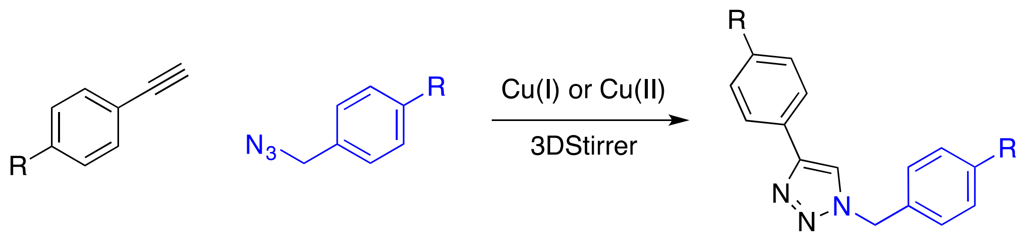


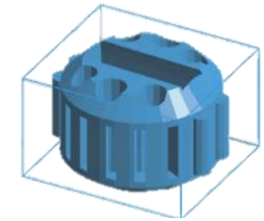
Catalyst	Yield (%)					
	$Sc(OTf)_3$	$Yb(OTf)_3$	CuOTf	$Y(OTf)_3$	$In(OTf)_3$	$Zn(OTf)_2$
Normal Stirrer + Powdered Catalyst	61	36	25	23	49	37
3D Stirrer Bead + Powdered Catalyst	64	54	33	25	62	52
Catalyst impregnated 3D Stirrer Bead	78	76	37	34	65	56

Rumintha Thavarajah

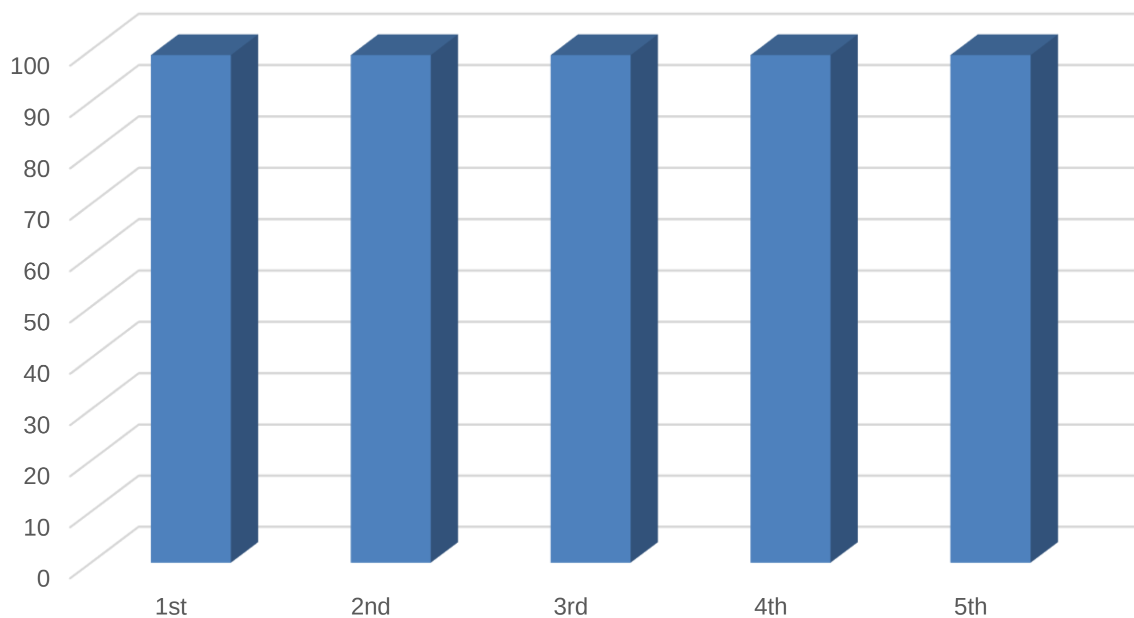
3DSynthesis Catalytic Stirrer Beads

Click Chemistry





Reuse of Copper Click Catalytic Stirrer Beads

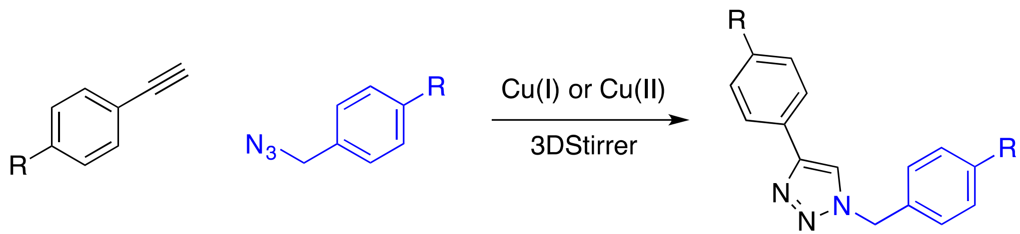


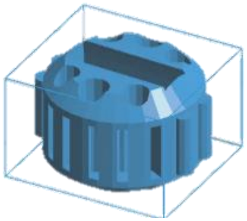
Moussa Sehailia

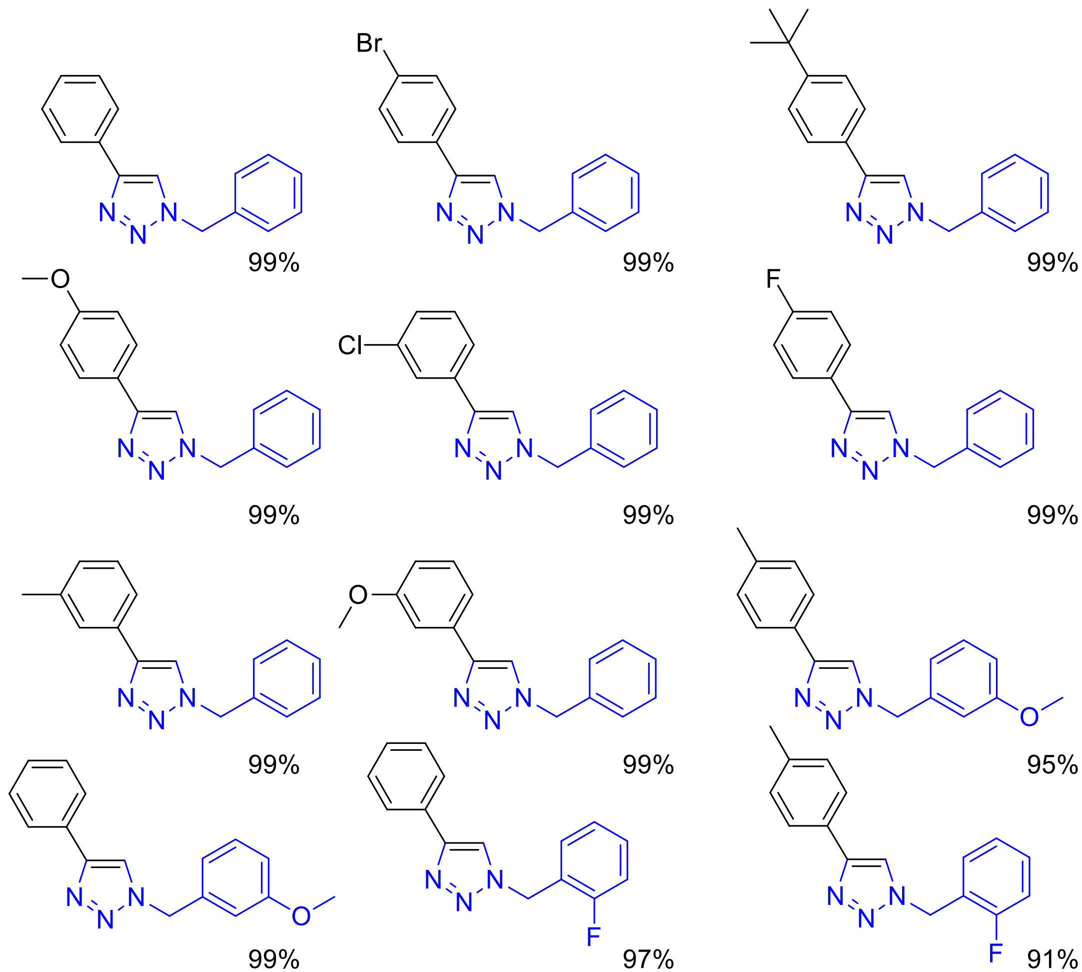
UCL SCHOOL OF PHARMACY
BRUNSWICK SQUARE

3DSynthesis Catalytic Stirrer Beads

Click Chemistry



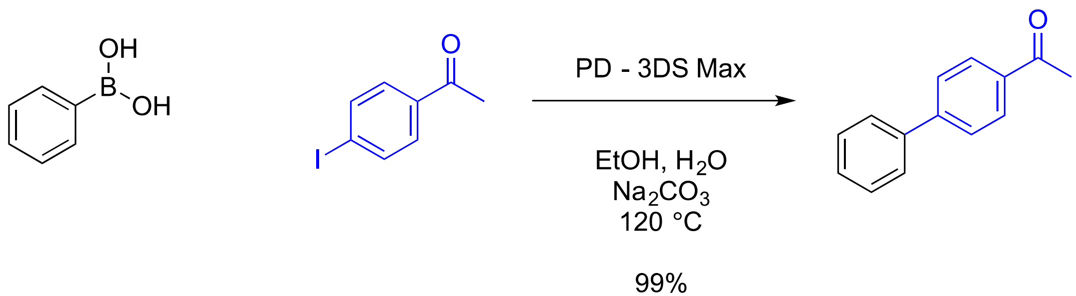


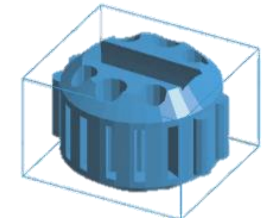


Moussa Sehailia

3DSynthesis Catalytic Stirrer Beads

Palladium Chemistry





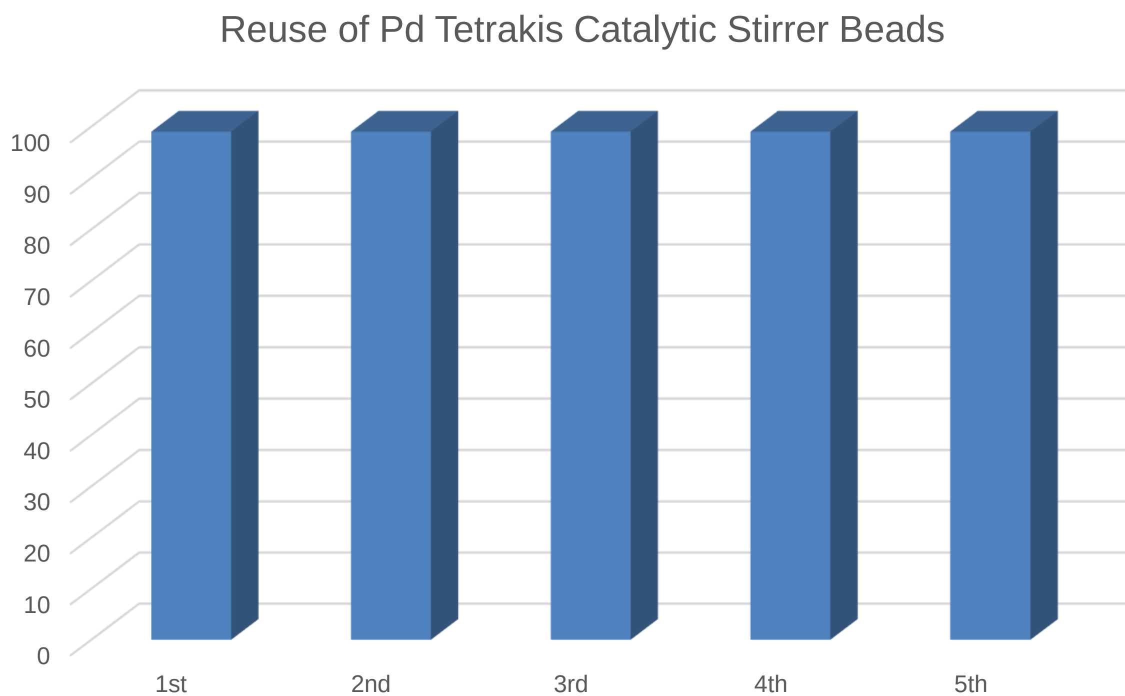
Suzuki coupling

0.25% Loading of Tetrakis $Pd(PPh_3)_4$ Per bead

Stable at room temperature

Reusable up to 5 times

Average 99%



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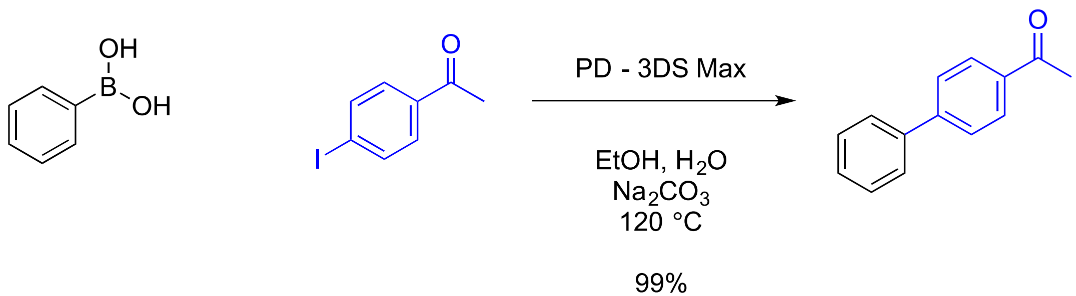
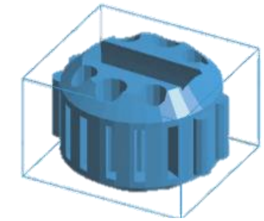
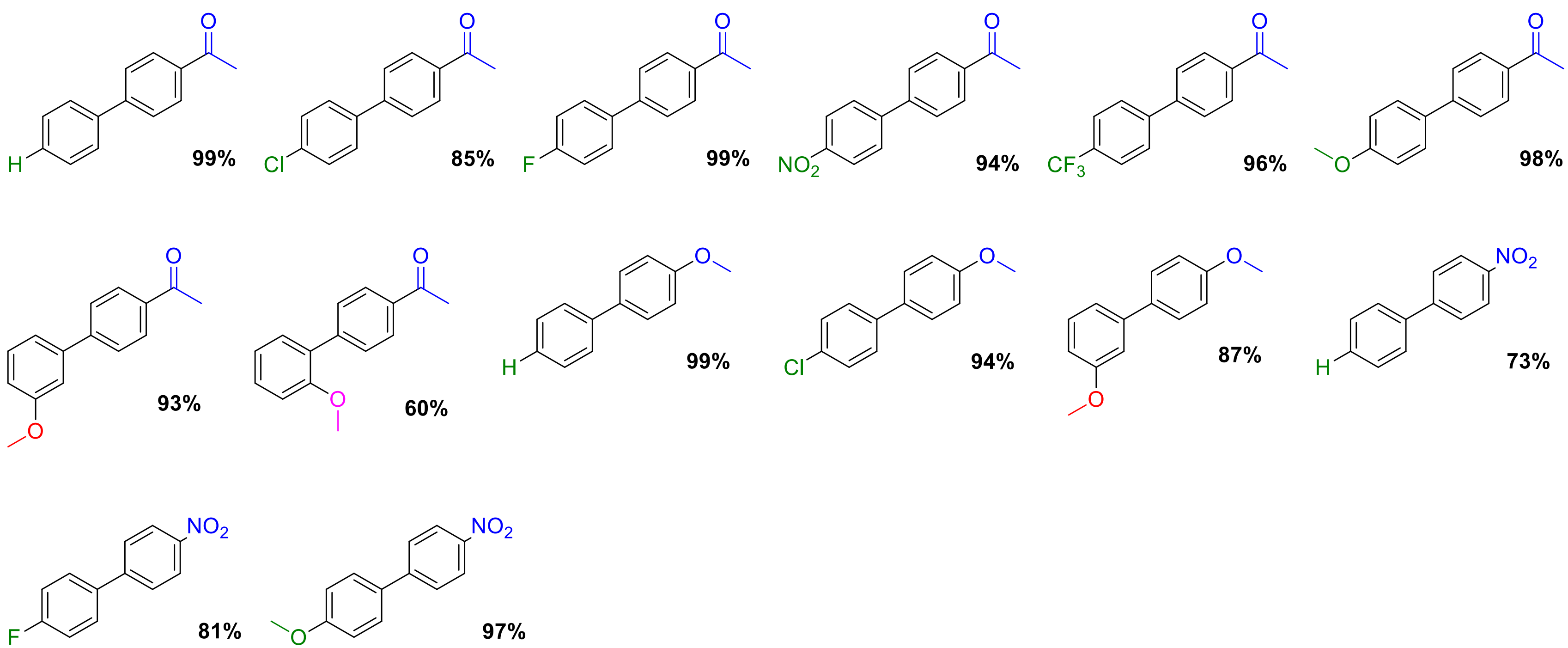
3DSynthesis Catalytic Stirrer Beads

Palladium Chemistry







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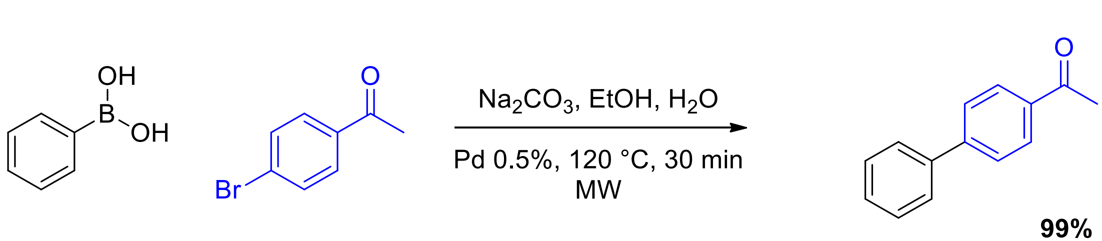
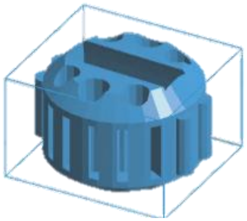
3DSynthesis Catalytic Stirrer Beads

Palladium Chemistry



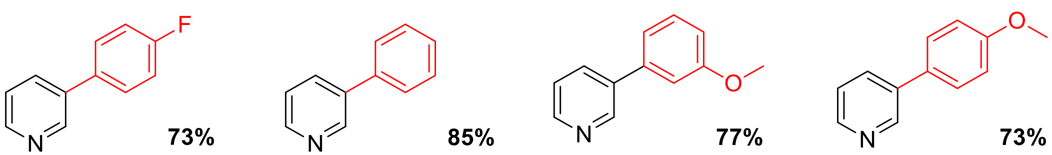


Microwave acceleration/ enhancement

Suzuki coupling

Bromides – lower Yielding

Microwave – reduction in time – 12 hours to 20-30 minutes



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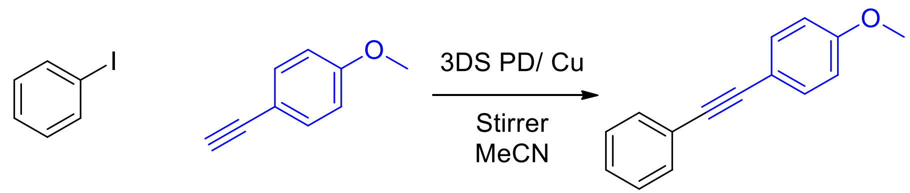
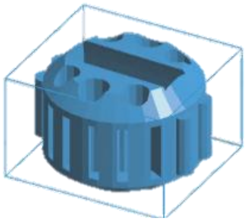
3DSynthesis Catalytic Stirrer Beads

Sonogashira Coupling

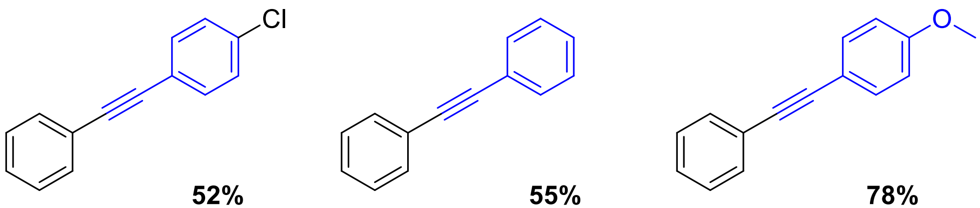




Microwave Reaction

Combination of Pd and Copper catalysts in the same bead

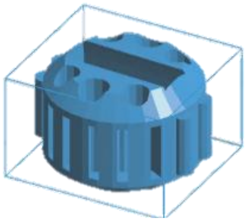
2 hours 50-80% yields



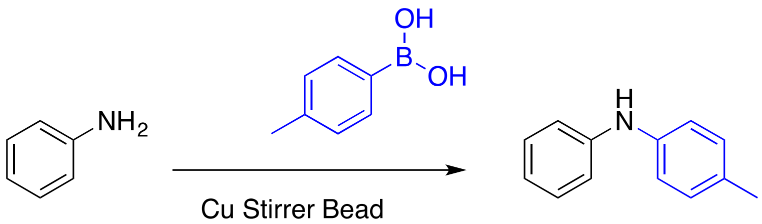
Rumintha Thavarajah

3DSynthesis Catalytic Stirrer Beads

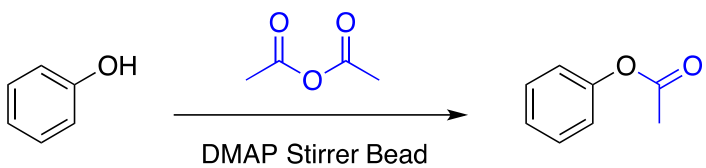
Additional Reactions



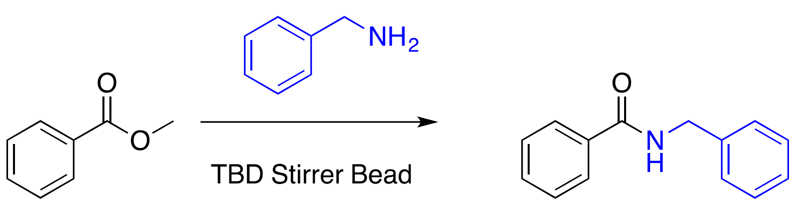
Chan Lam



Ester Formation



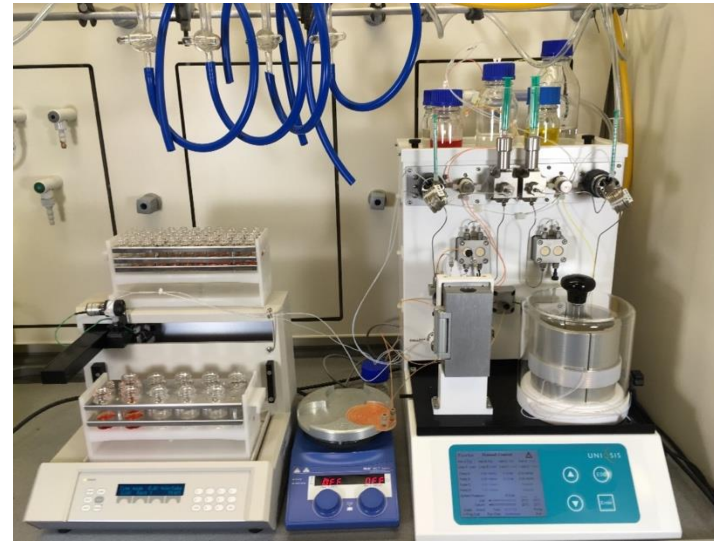
Amide Formation



Matthew Penny

Flow Chemistry – Reactor Types

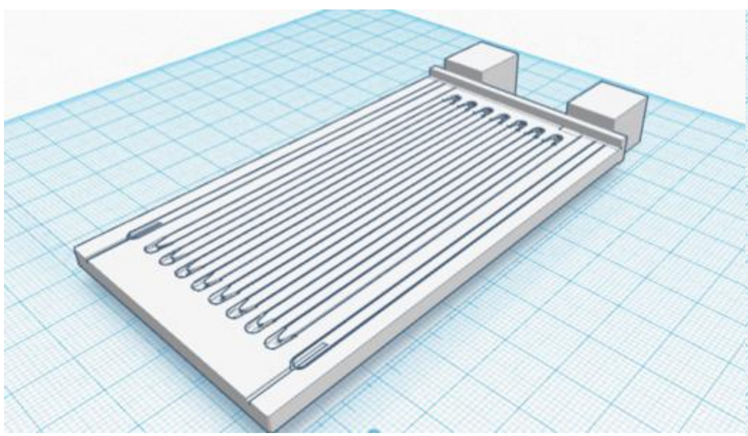
Reactor Design

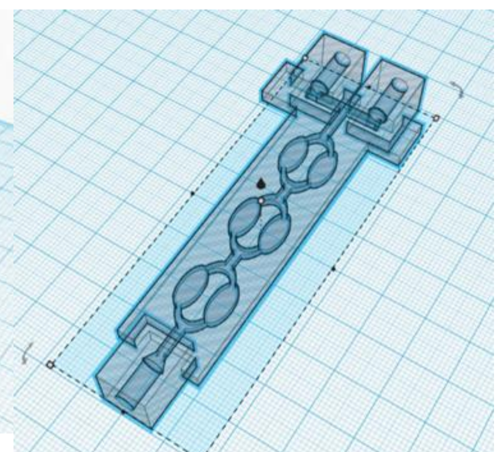


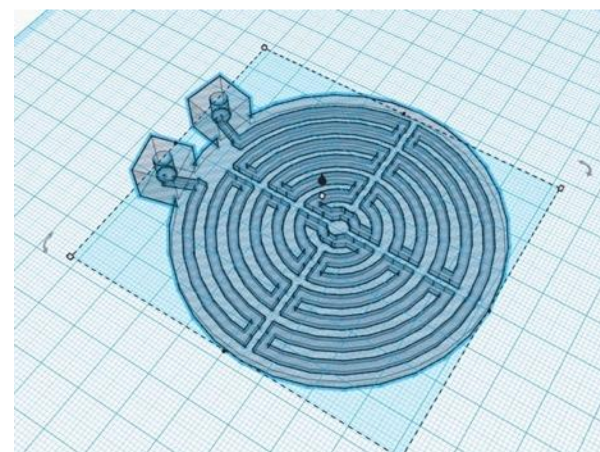
Ability to Print any shape and reactor size

Incorporation of PEEK fittings/ screw threads

Resistant to solvent







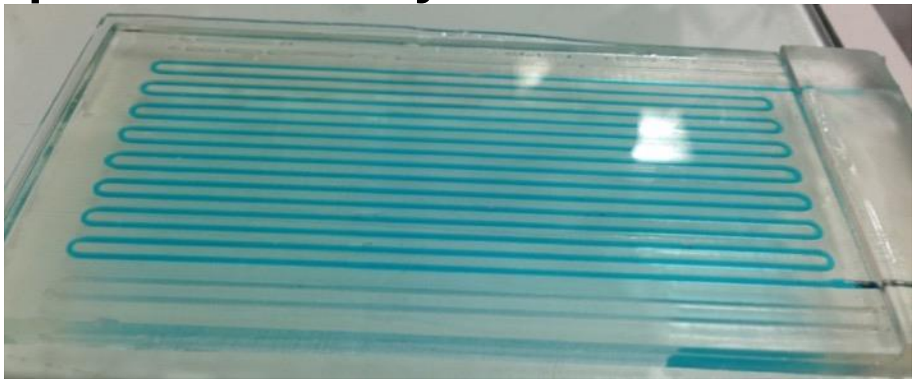
Zenobia Rao

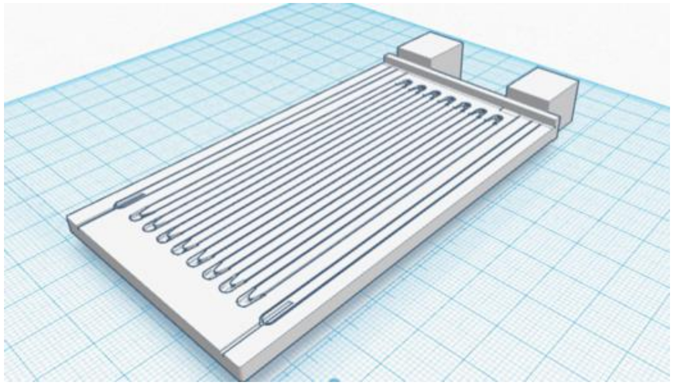
Photochemical Flow Reactors

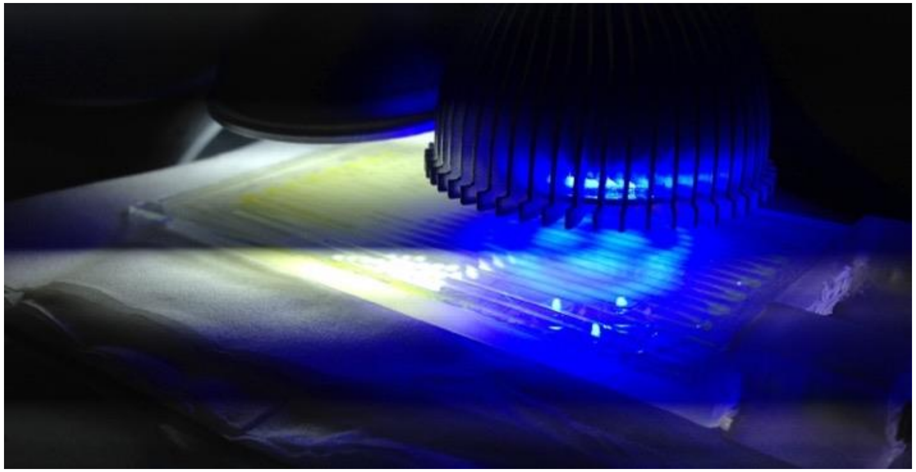
Extension into Flow Chemistry

Chemically Inert Polymer

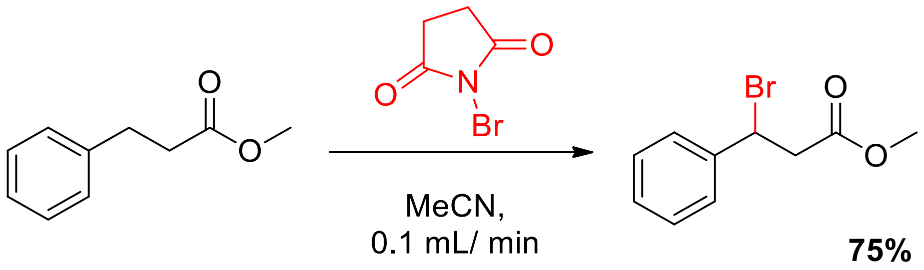
Flow Photochemistry via attachment to glass top over reactor bed – DCE as solvent in photodecarboxylation

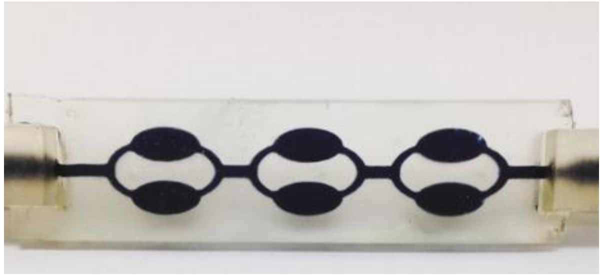






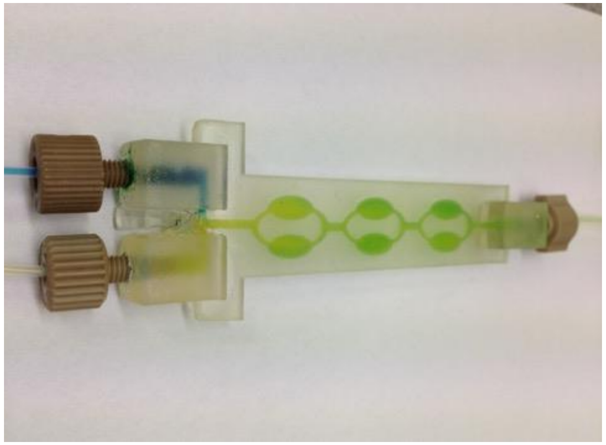
Catalytic Flow Reactors



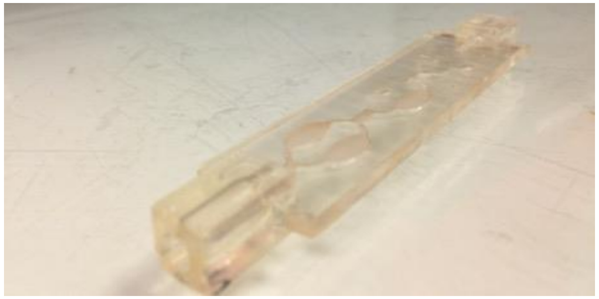


Single Split-wide reactor

Actinic bulb – scale up via additional Reactors



Catalytic reactors – containing Zinc triflate



J. Org. Chem. **2014**, 79, 223-229

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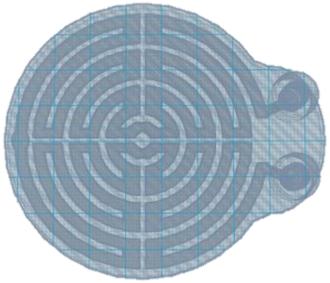
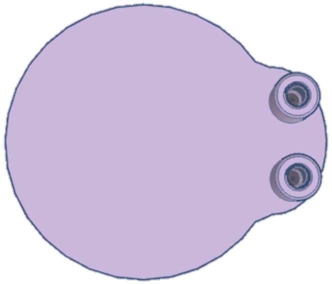
DrySyn Flow Reactors





- Flow Photochemistry
- Catalytic Flow Chemistry
- Stable up to 20 bar
- Readily configurable
- Built and designed with peek fitting threads
- Can be easily linked
- Modified flow path

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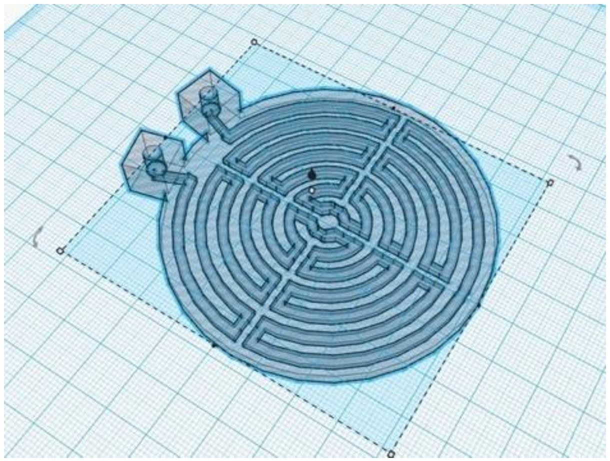
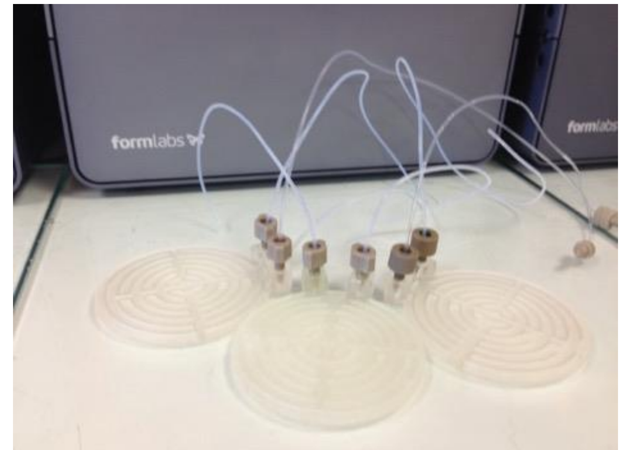
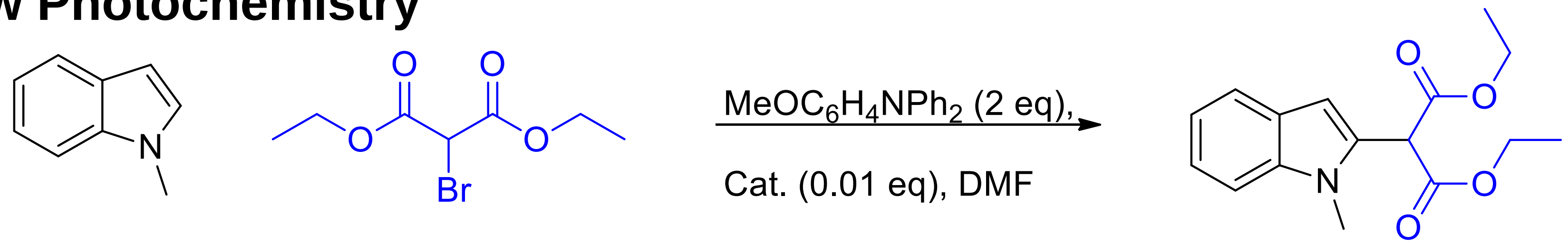
DrySyn Flow Reactors for Catalysis in Flow using Impregnated Catalysts



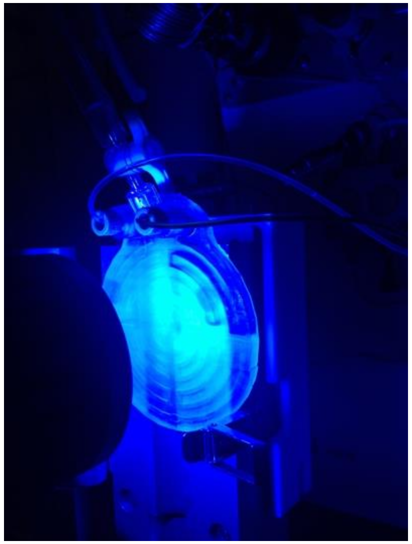


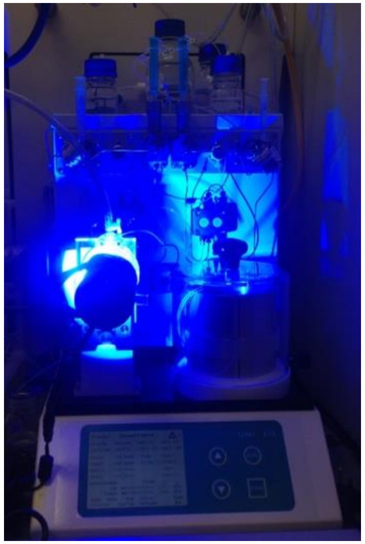
Flow Photochemistry

Flow Photochemistry



- Suitable with DMF- 16 bar pressure
- Actinic bulb with cooling
- Flow rates 0.1 - 0.05mL/min
- Yields ~80%





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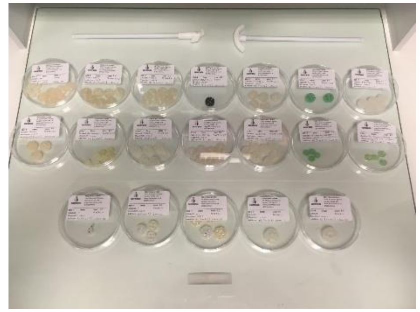
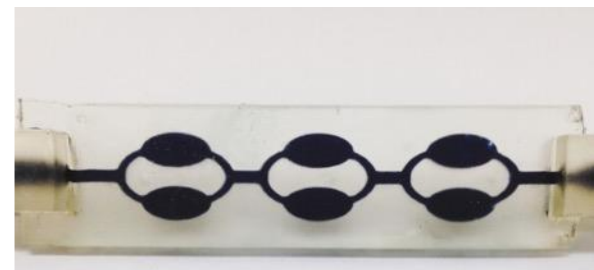
Summary

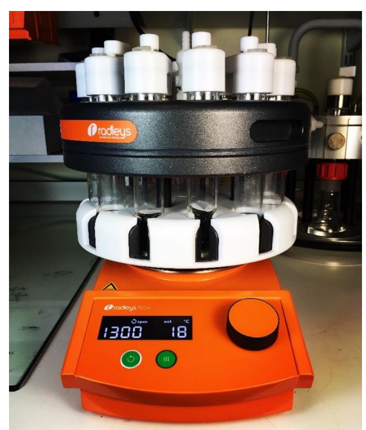
3D Printed And Catalysis



Great potential in the efficient catalysis of a wide array of reaction classes.

Low cost and applicable to both batch and continuous flow





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The Bloomsbury Colleges University of London
Nuffield Foundation
FCT Fundação para a Ciência e a Tecnologia
LLR-G5
Petplan the pet people
FNSNF Fonds national suisse Schweizerischer Nationalfonds Fondo nazionale svizzero Swiss National Science Foundation
UCLB